TOTAL SYNTHESIS OF (±)-KELSOENE AND SYNTHETIC APPROACHES TO (±)-ISOMULINIC ACID

by

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We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

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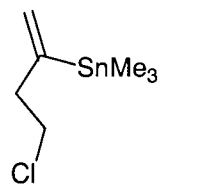
ABSTRACT

The total synthesis of the unique tricyclic terpene natural product (±)-kelsoene was achieved in 15 steps from commercially available cyclopent-2-en-1-one (**418**) and the bifunctional reagent 4-chloro-2-trimethylstannylbut-1-ene (**32**). Bicycle ***rac*-34** was constructed in two steps from enone **418** and served as the diquinane core of the natural product. The relative configuration of the carbon chirality center at C-8 was established through a highly diastereoselective homogeneous hydrogenation of ***rac*-34** using Wilkinson's catalyst. Compound ***rac*-59** was converted to enone ***rac*-61** in four steps using established methods. A highly diastereoselective [2+2]-photocycloaddition of ethylene to enone ***rac*-61** served to construct the four-membered ring of ketone ***rac*-64** and establish the carbon chirality centers at C-2 and C-5. Ketone ***rac*-64** was converted to alkene **143** using Lombardo's reagent. Hydroboration of alkene **143** and subsequent oxidation of the resulting material furnished alcohol **144**. This material was transformed into (±)-kelsoene in five steps using established methods.



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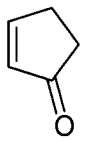

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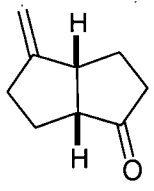

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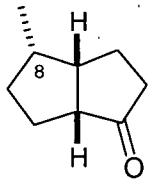

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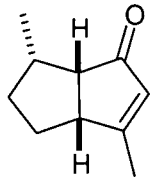

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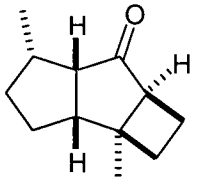

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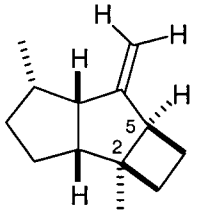

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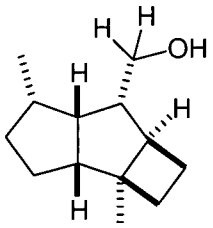

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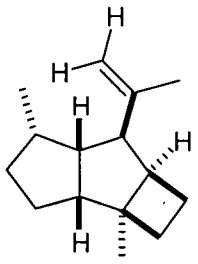


(±)-kelsoene

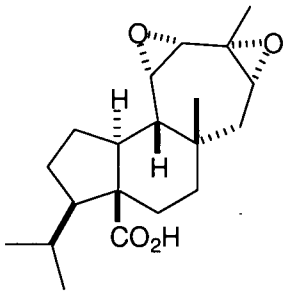
The total synthesis of the tricyclic sesquiterpenoid natural product (±)-isomulinic acid (**39**) was attempted using four distinct strategies.

Bicyclic enone **193** has the correct relative configuration at C-3 and C-5 and served as the platform for all the synthetic approaches attempted. Keto ester **189** was constructed from enone **193** in 8 steps. The alkylation of keto ester **189** with bifunctional reagent **36** furnished compound **226**, which has the incorrect relative configuration at C-10, as the major product.

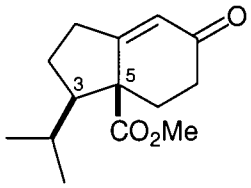
Alkene **228** was viewed as a key intermediate in the second synthetic approach to (±)-isomulinic acid. It was hoped that a highly diastereoselective [2+2]-photocycloaddition of **228** to a suitable partner would furnish a tricyclic such as **229**. Ketone **249** was prepared from enone **193** in 5 steps but did no yield access to alkene **228**. Similarly, alkene **273** was constructed from enone **193** in 6 steps but did not yield access to alkene **228**.

Enone **293** was efficiently prepared from enone **193** and was transformed into ketone **299** through a heterogeneous hydrogenation. Although ketone **299** possesses the correct relative configuration at C-9 and C-10, it could no be prepared in large scale due to its instability under the conditions used for its preparation.

Ketone **309** was prepared from enone **193** using a sequence of reactions similar to those used to prepare ketone **299**. Ketone **309** was elaborated to a bicycle **377**, using a 12-step sequence of reactions. Due to an unforeseen side reaction, the ettempted homologation of the aldehyde moiety of **377** resulted in the formation of aldehyde **398**. It could be shown that tricycle **402** could be prepared from **398**.



(±)-isomulinic acid (39)



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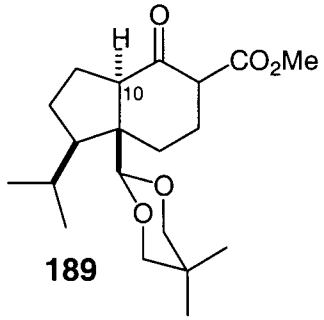

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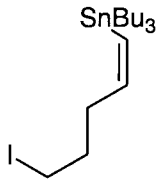

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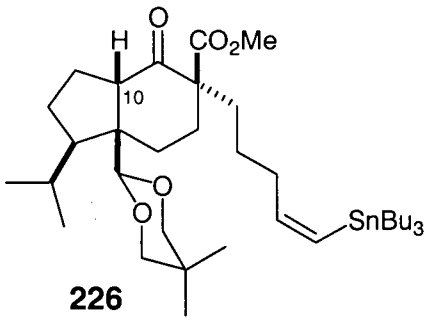

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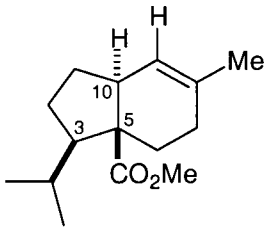

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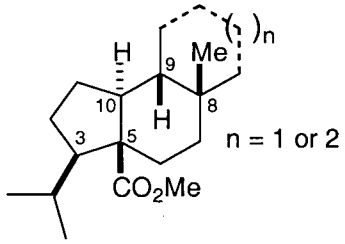

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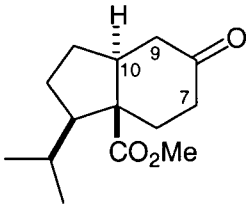

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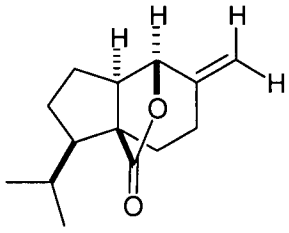

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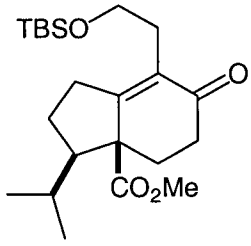

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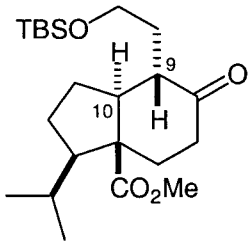

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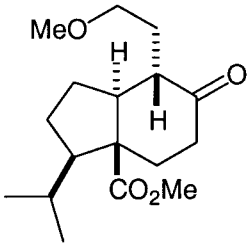

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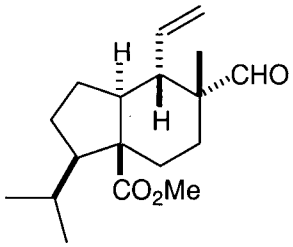

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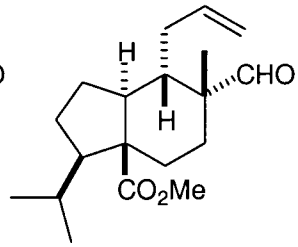

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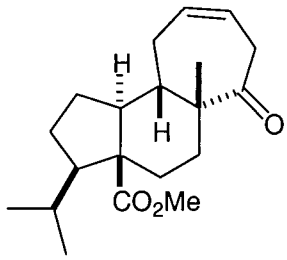

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LIST OF SYMBOLS AND ABBREVIATIONS

1D	-	one-dimensional
^{1}H	-	proton
^{2}H	-	deuterium
^{13}C	-	carbon-13
9-BBN	-	9-Borabicyclo[3.3.1]nonane
α	-	below the plane of a ring or 1,2 relative position
β	-	above the plane of a ring or 1,3 relative position
δ	-	chemical shift in parts per million or 1,5 relative position
Δ	-	reflux
γ	-	1,4 relative position
λ	-	wavelength
µm	-	micrometer
AcOH	-	acetic acid
APT	-	Attached Proton Test (see *J*-mod)
aq	-	aqueous
ax	-	axial
br	-	broad
BF_3•Et_2O	-	boron trifluoride-dimethyl etherate complex
BH_3•SMe	-	borane-dimethyl sulfide complex
BH_3•THF	-	borane-tetrahydrofuran complex
BuLi	-	butyllithium
°C	-	degrees Celsius
calcd.	-	calculated
cm	-	centimeter
COSY	-	(^{1}H-^{1}H)-homonuclear correlation spectroscopy
CuBr•DMS	-	copper(I) bromide-dimethyl sulfide complex
CuCN	-	copper(I) cyanide
CuI	-	copper(I) iodide
CuOTf	-	copper(I) trifluoromethanesulfonate

LIST OF SYMBOLS AND ABBREVIATIONS – Continued

C-X	-	carbon number X
d	-	doublet
DBU	-	1,8-diazabicyclo[5.4.0]undec-7-ene
DCI	-	deuterium chloride
DCM	-	dichloromethane
DIBAL-H	-	diisobutylaluminum hydride
DMAP	-	4-dimethylaminopyridine
DMDO	-	dimethyl dioxirane
DME	-	dimethoxyethane
DMF	-	*N,N*-dimethylformamide
DMSO	-	dimethyl sulfoxide
E	-	entgegen (configuration)
ee	-	enantiomeric excess
ent	-	enantiomeric
eq	-	equatorial
equiv.	-	equivalents
EtOAc	-	ethyl acetate
EtOH	-	ethanol
Et_2O	-	diethyl ether
g	-	grams(s)
GC	-	gas chromatography
GC-LRMS	-	coupled gas chromatography-low resolution mass spectrometry
GC-MS	-	coupled gas chromatography-mass spectrometry
GLC-MS	-	coupled gas-liquid chromatography-mass spectrometry
h	-	hours(s)
HCl	-	hydrochloric acid
HMBC	-	^{1}H detected multiple bond heteronuclear multiple quantum Coherence
HMPA	-	hexamethylphosphoramide

LIST OF SYMBOLS AND ABBREVIATIONS – Continued

HMQC	-	^{1}H detected heteronuclear multiple quantum coherence
HOAc	-	acetic acid
HREIMS	-	high resolution electron impact mass spectrometry
HRMS	-	high resolution mass spectrometry
hυ	-	light energy
Hz	-	hertz (s^{-1})
IR	-	infrared
J	-	coupling constant in hertz
J-mod	-	*J*-modulated spin echo (see APT)
$^{n}J_{Sn-H}$	-	n bond coupling constant between tin and proton nuclei (in hertz)
KH	-	potassium hydride
KHMDS	-	potassium bis(trimethylsilyl)amide
KOH	-	potassium hydroxide
LDA	-	lithium diisopropylamide
LHMDS	-	lithium bis(trimethylsilyl)amide
LiBr	-	lithium bromide
LiCl	-	lithium chloride
m	-	meter(s)
M	-	Molar
M^{+}	-	molecular ion
MABR	-	methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide)
MCPBA	-	*meta*-chloroperbenzoic acid
Me	-	methyl
MeCN	-	acetonitrile
MeI	-	iodomethane, methyl iodide
MeLi	-	methyllithium
MeOH	-	methanol
Mg	-	milligram(s)
MHz	-	megahertz

LIST OF SYMBOLS AND ABBREVIATIONS – Continued

min	-	minute(s)
mL	-	milliliter(s)
mm	-	millimeter(s)
mmol	-	millimole(s)
mol	-	mole(s)
mp	-	melting point
NaH	-	sodium hydride
NaOAc	-	sodium acetate
NaOH	-	sodium hydroxide
NaOMe	-	sodium methoxide
NMO	-	*N*-methylmorpholine *N*-oxide
NMR	-	nuclear magnetic resonance
NOE	-	nuclear Overhauser effect
PCC	-	pyridinium chlorochromate
PDC	-	pyridinium dichromate
PhH	-	benzene
PhSeCl	-	phenylselenenyl chloride
PPL	-	porcine pancreatic lipase
ppm	-	parts per million
psi	-	pounds per square inch
p-TSA	-	*para*-toluenesulfonic acid
q	-	quartet
R	-	rectus (configuration)
rac	-	racemic
s	-	singlet
S	-	sinister (configuration)
r.t.	-	room temperature
sat.	-	saturated
TBSCl	-	*tert*-butyldimethylsilyl chloride

LIST OF SYMBOLS AND ABBREVIATIONS - Continued

t	-	tripet
t	-	tertiary
TBAF	-	tetrabutylammonium fluoride
TBDMSCl	-	*tert*-butyldimethylsilyl chloride
t-BuOH	-	*tert*-butyl alcohol
t-BuOK	-	potassium *tert*-butoxide
t-BuOMe	-	*tert*-butyl methyl ether
tert	-	tertiary
TFA	-	trifluoromethanesulfonic acid
THF	-	tetrahydrofuran
TLC	-	thin layer chromatography
TMSCl	-	trimethylsilyl chloride, chlorotrimethylsilane
TMSI	-	trimethylsilyl iodide, iodotrimethylsilane
TMSOTf	-	trimethylsilyl trifluoromethanesulfonate
TOCSY	-	total correlation spectroscopy
TPAP	-	tetrapropylammonium perruthenate
TsCl	-	*para*-toluenesulfonyl chloride
UBC	-	University of British Columbia
UV	-	ultraviolet
–ve	-	negative
+ve	-	positive
W	-	watts
Z	-	zusammen (configuration)
±	-	racemic

ACKNOWLEDGEMENTS

The completion of this thesis brings to a close a remarkable six-year period in my life. A great many people have influenced me in ways that neither they nor I imagined.

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Bianca, Jenny, Mom and Dad; I could not have persevered without your love, support and inspiration.

Este tesis es dedicado, con mucho cariño, a mi familia

1. Introduction

1.1 General

1.1.1 Origins of Organic Chemistry[1,2]

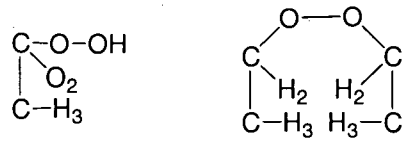
Until the late 1700s organic chemistry was a primitive science. Indeed, no one could claim to know how organic and inorganic chemicals differed. Some even believed that organic chemicals possessed a vital force and could not be prepared in the laboratory. In 1786 Lavoisier defined organic chemicals as combinations of oxygen with radicals that contained carbon and hydrogen. If the compounds were of animal origin, then they could also contain nitrogen and phosphorous. He did not, however, specify what a radical was.

It was not until 1828, with Friedrich Wohler's preparation of urea from ammonium cyanate, that the notion of a vital force began to lose credence. Conclusive evidence against this concept was provided in 1845 by Kolbe and Berthelot, who were able to synthesize organic compounds directly from the elements. Some argue that Wohler's preparation of urea marks the birth of synthetic organic chemistry. However, the lack of an understanding of the relationship between carbon, hydrogen and other elements suggests that the emergence of synthetic organic chemistry as a rigorous science occurred much later.

New theories addressing the nature of organic compounds began to emerge in the second part of the 19th century. The first breakthrough came in a report entitled "A New Chemical Theory" authored in 1858 by Archibald Scott Couper. In it, the 27 year old stated:

> I propose to consider the single element carbon. This body is found to have highly distinguished characteristics: 1. It combines with equal numbers of equivalents of hydrogen, chlorine, oxygen, sulfur, etc. 2. It enters into chemical union with itself. These two properties in my opinion explain all that is characteristic of organic chemistry.

Although obscure, Couper's report was revolutionary. He defined structure as the connection between atoms to form molecules (**Figure 1.1**) at a time when Kekulé considered the concept of atoms a "convenient fiction". He even speculated on the composite nature of the atom 40 years before the work of J. J. Thompson. Unfortunately, Couper's work remained neglected until 1900 and, in the meantime, Kekulé's ideas formed the basis for work on structural covalent chemistry.



1 **2**

Figure 1.1: Couper's formulas for acetic acid (1) and ethyl ether (2)

Ideas regarding the tetravalent nature of the carbon atom and its implications to the structure of organic materials were advanced by Pasteur in 1860, Butlerow in 1862, and (surprisingly) Kekulé in 1867. They did not gain credibility until 1874 when Van't Hoff and Le Bel, in an attempt to explain optical activity, independently proposed that a tetrahedral carbon atom with four different substituents could exist in two forms. In spite of skeptics like Kolbe, who proclaimed that these ideas were "not far removed from belief in witchery and ghost-rapping", Van't Hoff's views were widely accepted by 1894, except by those who did not embrace the atomic hypothesis. This situation would change upon the revolution in physics which demonstrated the existence of an atom and its composite nature.

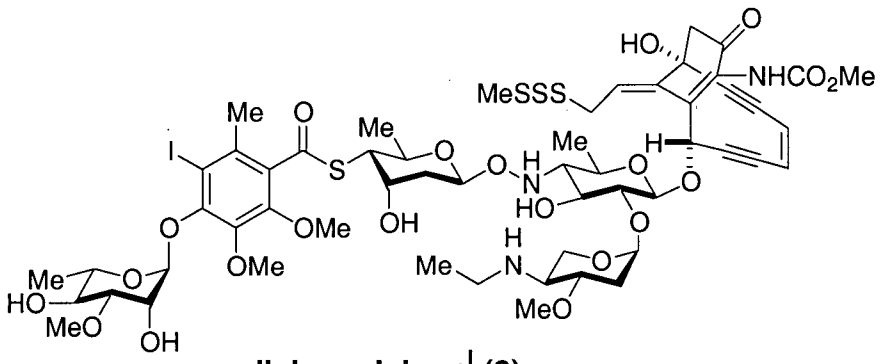
1.1.2 Organic Chemistry in the 20th Century

Organic chemistry flourished in the last century and is now, by most measures, a mature science. The Nobel Prize for Chemistry[3] serves as a convenient chronicle of major achievements in the field. A comment on the state of the art in organic chemistry is provided in the 1912 lectures. In his presentation speech Söderbaum[4] claimed that "no method of organic synthesis superior to that of Grignard's is known", and queried if we would "ever learn how to produce artificially alkaloids or vegetable organic bases?" Grignard[5] had a more positive outlook and hinted at advances to come; he noted

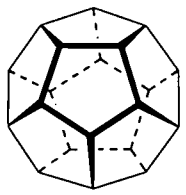
> ...a new group of very interesting syntheses, namely asymmetrical synthesis....(McKenzie) esterified benzoylformic, pyruvic and laevulic acids by *l*-menthol, and he caused the organic magnesium compound to react with the CO of each of these active esters. Then by saponifying the products obtained in order to eliminate the menthol he obtained slightly levorotatory alcohol acids.

It would have been difficult for Grignard and Söderbaum to imagine the breakthroughs that would occur in organic chemistry during the remainder of the century. The number of methods available to the synthetic chemist has grown at an intimidating rate and was estimated to be greater than 35,000 in 1990.[6] The Swedish Royal Academy of Sciences has recognized contributions in this area on a number of occasions. Notable recipients of the prize include Alder and Diels[7] for their "discovery and development of the synthesis of dienes," Brown[8] for his work on borohydrides and organoboranes, and Wittig[8] for the development of phosphorous ylides. Methods for asymmetric synthesis abound, and for their work in this field Knowles,[9] Noyori[10] and Sharpless[11] received the Nobel Prize in 2001.

The synthesis of organic materials is no longer viewed with the pessimism of Söderbaum. To conceive molecules of such astonishing complexity as calicheamicin γ_1^I (**3**)[12] and awesome symmetry as dodecahedrane (**4**) (**Figure 1.2**), would have been difficult in 1912, and their chemical synthesis[13-15] would have been unimaginable. Yet, by the 1960's the art of organic synthesis had reached new heights, and in 1965 Woodward's sophisticated contributions were acknowledged with the Nobel Prize. Thirty five years later Corey was credited with "turning the art of chemical synthesis into a science".[6]



calicheamicin $\gamma 1^{I}$ (3)



dodecahedrane (4)

Figure 1.2: Impressive structures of calicheamicin γ_1^{I} (3) and dodecahedrane (4)

These accomplishments by no means indicate that organic chemistry is a dying science.[16] The need to develop new methods and strategies for the construction of organic compounds is continually fueled by the elucidation of novel structures found in nature. Moreover, Wender's notion of the "ideal synthesis"[17] and Trost's concept of "atom economy"[18] remain lofty goals, and the most celebrated synthetic achievements often exceed the 25-step "rational limit" proposed by Hudlicky.[19]

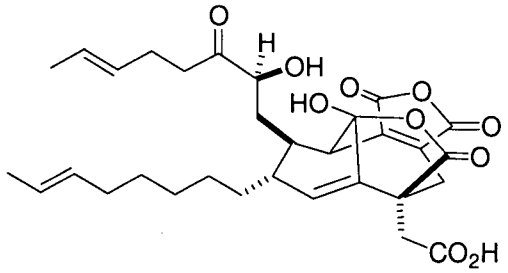
1.2 Creativity in Total Synthesis

The total synthesis of natural products has occupied a prominent position in the field of organic chemistry over the last half century, and many accounts outlining the value of this exercise have been published. Experience teaches that there is arguably no better training ground for young synthetic organic chemists than the total synthesis of a challenging natural product. Furthermore, the complexity of the target molecule may be such that the development of new synthetic methods or the formulation of an innovative synthetic strategy may be required. Often, a total synthesis serves as a rigorous test for a newly developed synthetic method. There are even some, including this author, who argue that the total synthesis of natural products has intrinsic value as a form of art.

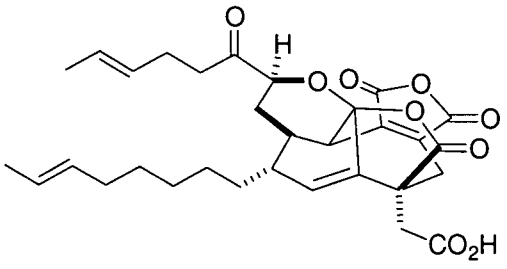
Synthetic chemists express their creative spirit in various forms. Some choose to construct a target in the most ingenious ways, often assembling intricate structures

through a series of transformations occurring in a single synthetic operation. Others approach the challenge of a daunting synthesis with a sense of adventure, and cherish the opportunity to develop new technology during the journey. Natural products which possess both elaborate carbocyclic frameworks and unusual functionality, and which display potentially useful biological activity, are the targets of choice for total synthesis. An instructive example follows.

In 1995 the two novel structures known as CP-225,917 (**5**) and CP-263,114 (**6**) were disclosed[20,21] and immediately attracted the attention of synthetic chemists (**Figure 1.3**). The key structural features embedded in these molecules include a bicyclo[4.3.1]decane system, a bridgehead double bond, a maleic anhydride, a γ-hydroxylactone, an α-hydroxyketone and a quaternary center. The γ-hydroxylactone and the α-hydroxyketone moieties found in CP-225,917 combine to form a tetrahydropyran system in CP-263,114.



(+)-CP-225,917 (5)



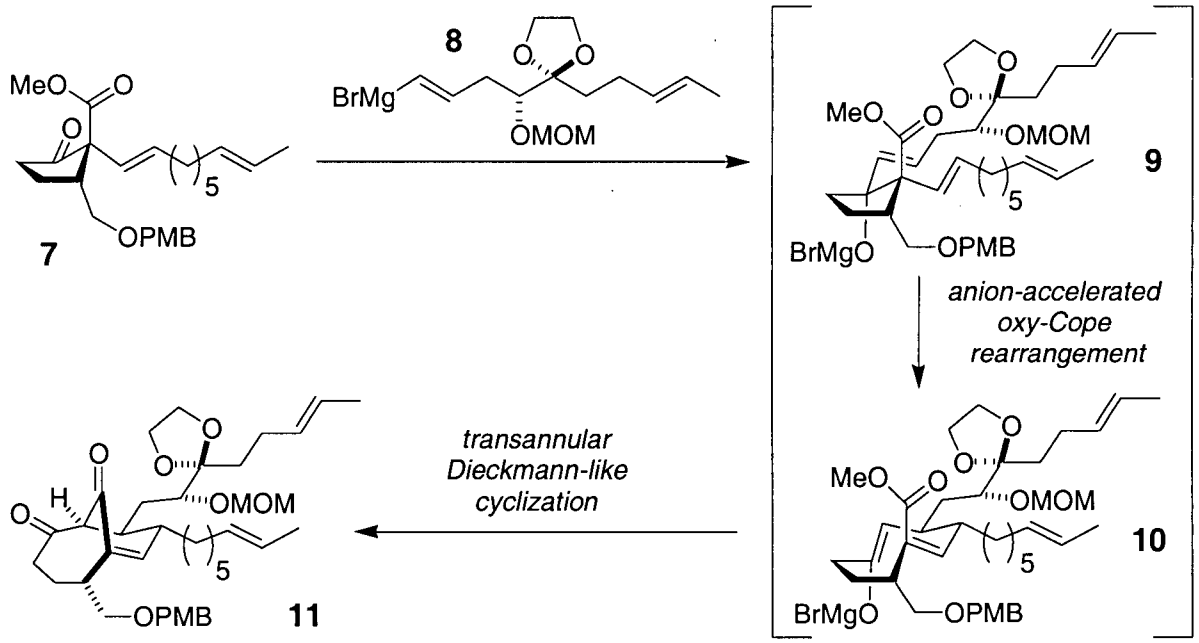
(-)-CP-263,114 (6)

Figure 1.3: Structure of the CP molecules

Both CP-225,917 and CP-263,114 inhibit squalene synthase and farnesyl protein transferase. Squalene synthase catalyzes the condensation of two molecules of farnesyl pyrophosphate to squalene, an intermediate in the biosynthesis of cholesterol. Thus, it is possible that the CP molecules may lead to new cholesterol lowering drugs. Farnesyl protein transferase mediates farnesylation of the protein p21. Mutated p21 is rendered permanently active and thus leads to unregulated cell growth and division. As farnesyl protein transferase inhibitors, the CP molecules may interfere with a step crucial to p21 activity and the carcinogenic process. Clearly, these molecules are ideal targets for total synthesis.

A significant body of literature related to the synthesis of the CP molecules exists, however the work of Shair[22,23] is conspicuous for its creativity. Shair's approach to (+)-CP-263,114 (***ent*-6**) is ingenious on two counts: 1. His incisive retrosynthetic analysis allows the construction of a carbocycle reminiscent of the CP molecules from a relatively simple material in a single synthetic operation. 2. His conditions for establishing the quaternary carbon chirality center constitute a new method for chemical synthesis.

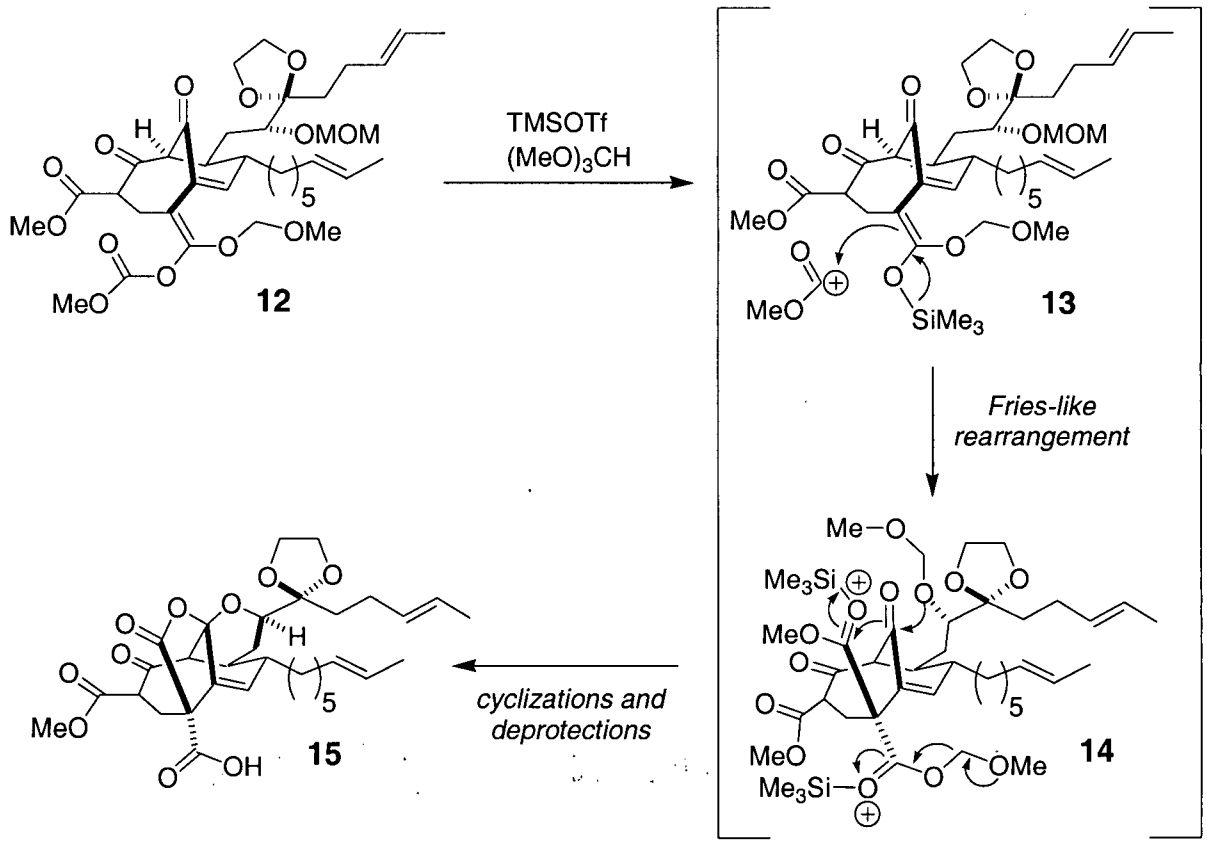
The enantiomerically enriched keto ester **7** is obtained in 3 steps from 2-iodocyclopent-2-en-1-one and the adduct resulting from its reaction with the Grignard reagent **8** undergoes a remarkable series of transformations (**Scheme 1.1**). The 1,5-diene embedded in bromomagnesium alkoxide **9** undergoes the well known anion accelerated oxy-Cope rearrangement, and yields a bromomagnesium enolate (**10**). This material collapses to diketone **11** upon a transannular Dieckmann-like cyclization.



Scheme 1.1: Construction of diketone 11 from keto ester 7[23]

The synthesis continues with the elaboration of diketone **11** to enol carbonate **12** in 6 steps. A likely mechanism for the number of transformations which result in the conversion of **12** into acid **15** is depicted in **Scheme 1.2**. Compound **12**, upon TMSOTf

promoted ionization of the enol carbonate moiety, releases a silylketene acetal (**13**) and a carbomethoxenium ion fragment. Recombination of these two units results in the formation of a new carbon-carbon bond in a manner reminiscent of the Fries rearrangement, and establishes the quaternary carbon chirality center. The resulting intermediate (**14**) undergoes a number of deprotection and cyclization reactions under the influence of TMSOTf, which culminate in the formation of polycyclic acid **15**. This material leads to the target compound in five synthetic operations.

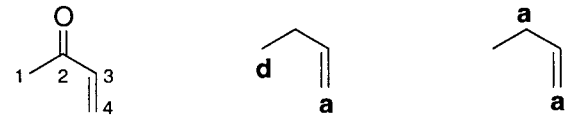


Scheme 1.2: Conversion of enol carbonate 12 to acid 15[23]

This relatively short synthesis of such a complex natural product was facilitated by the preparation of carbocycle **11**, which resembles the natural product, at an early point in the sequence. This, in turn, resulted from a penetrating retrosynthetic analysis which called for the use of three reactions, namely a Grignard addition, an anion accelerated oxy-Cope rearrangement and a Dieckmann-like cyclization, in a single synthetic operation. In addition, the challenge presented by the quaternary carbon chirality center resulted in the development of a new synthetic method.

1.3 Background

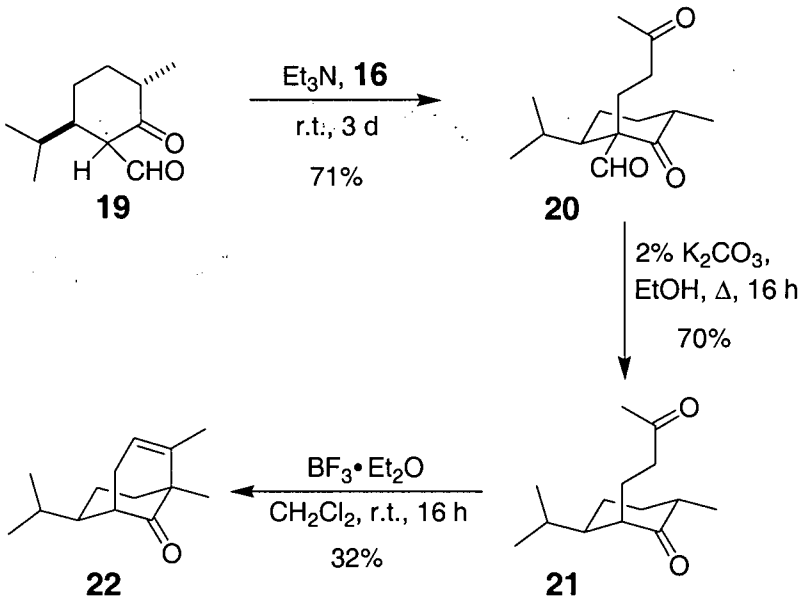
Many small molecules with two or more functional groups are useful in the construction of carbocycles. Methyl vinyl ketone (**16**, **Figure 1.4**) is perhaps the best known example of such compounds and its use in the Robinson annulation is a fundamental method for the construction of six-membered rings. The polar nature of the carbon-oxygen double bond imposes a reactivity pattern upon the carbon skeleton of methyl vinyl ketone. As a result, C-1 and C-3 have *donor* (**d**) properties, as defined by Seebach,[24] and are reactive towards electrophiles. Similarly, C-2 and C-4 have *acceptor* (**a**) properties and are susceptible to attack by nucleophiles. In the Robinson annulation, methyl vinyl ketone may be regarded as the synthetic equivalent of the but-1-ene a^1,d^4-synthon[25] (**17**).



16 **17** **18**

Figure 1.4: Methyl vinyl ketone as two different but-1-ene synthons

An annulation sequence developed by Corey and used in a synthesis of the natural product helminthosporal[26] demonstrates the (less common) use of this versatile reagent as a but-1-ene a^1,a^3-synthon (**18**, **Scheme 1.3**). Triethylamine promoted reaction of the (–)-carvomenthone derived keto aldehyde (**19**) with methyl vinyl ketone results in the axially alkylated material **20**, which is deformylated under mildly basic conditions to provide diketone **21**. Subjection of this diketone to Robinson annulation conditions would result in the fused bicycloalkenone product. In this example, treatment of **21** with $BF_3 \bullet Et_2O$ results in the formation of the bridged bicycle **22**. This mode of cyclization is observed as a side reaction in the Robinson annulation. Although the desired bridged bicycle was obtained and led to the synthesis of the target molecule, the low yield for this transformation (**21** to **22**) detracts from the utility of this method.



Scheme 1.3: The use of methyl vinyl ketone as a but-1-ene a^1,a^3-synthon[26]

The development of more sophisticated small molecules for the construction of carbocycles has been a research theme in this group for some time. Indeed, a significant number of bifunctional reagents have been prepared, and many have been featured prominently in the synthesis of natural products, including crinipellin[27] (**23**) and variecolin[28] (**24**, **Figure 1.5**).

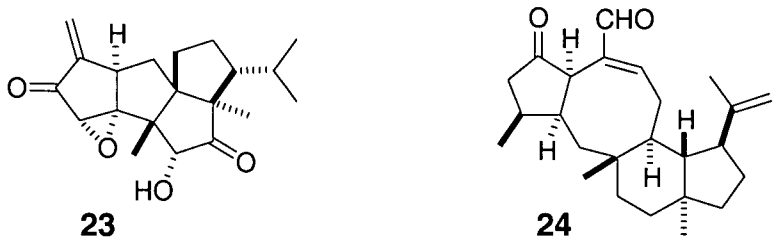
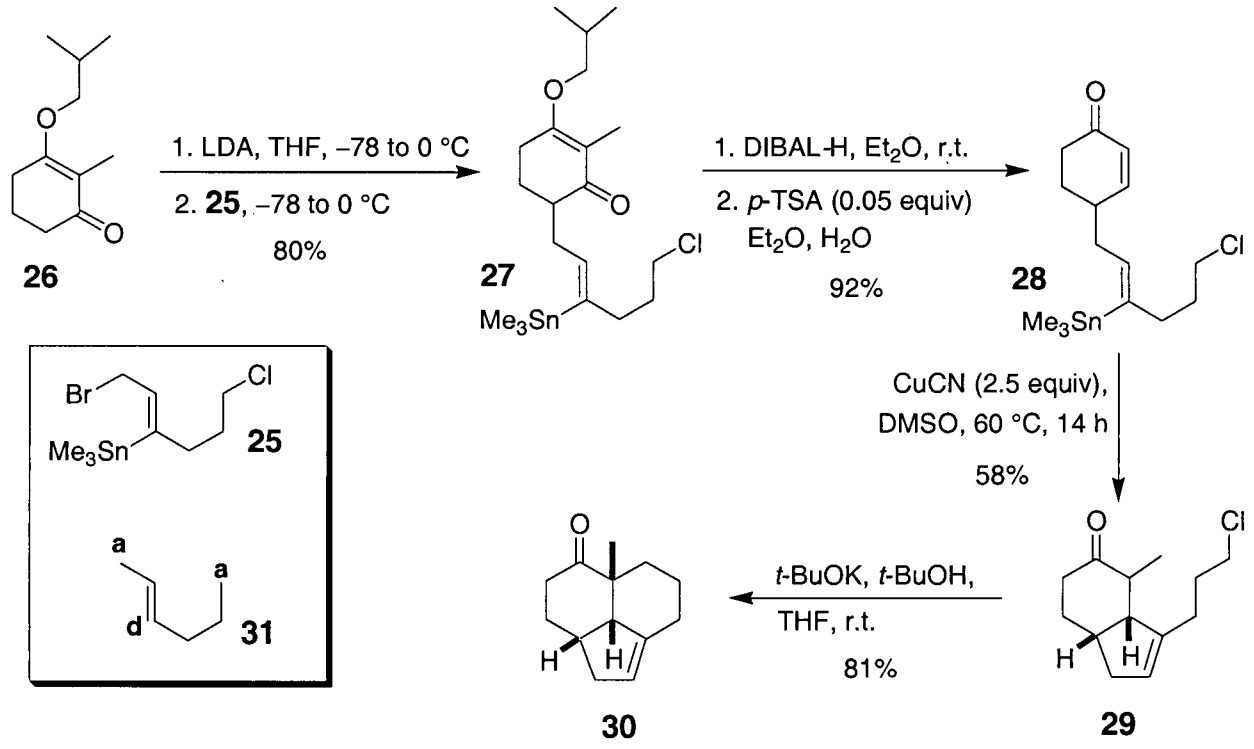


Figure 1.5: Structures of crinipellin (23) and varicolin (24)

In some cases trifunctional reagents[29] have served to construct relatively complex polycyclic materials using a short sequence of reactions (**Scheme 1.4**). Alkylation of vinyligous ester **26** with the trifunctional reagent **25** proceeds in good yield under standard conditions to generate compound **27**. Reduction of the carbonyl moiety in **27**, and treatment of the resulting material with a catalytic amount of acid reveals the

latent conjugated enone to provide **28**. Copper cyanide mediated intramolecular addition of the alkenyltrimethylstannane function to the α,β-unsaturated ketone results in the formation of the *cis*-fused bicycle **29**, albeit in modest yield. Finally, intramolecular alkylation of the potassium enolate derived from **29** provides the tricyclic compound **30** as a single diastereomer. Thus, the use of trifunctional reagent **25**, which served as the *trans*-hex-2-ene a^1,d^3,a^6-synthon (**31**), facilitated the preparation of carbocycle **30** from vinyligous ester **26** in only 5 synthetic operations.

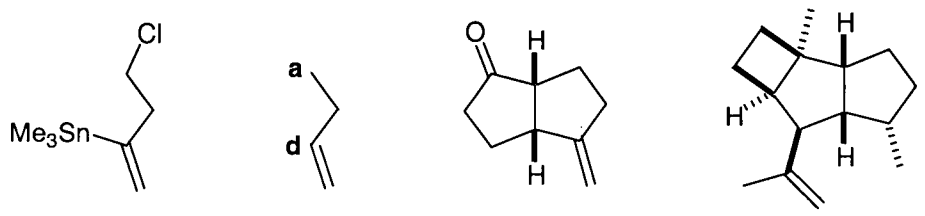


Scheme 1.4: Complex carbocycle construction using a trifunctional reagent[29]

1.4 Proposals

As part of a continuing effort to highlight the use of bifunctional reagents developed in this laboratory, two total synthesis projects were undertaken. The structure of the natural product (+)-kelsoene (**35**, **Figure 1.6**) was elucidated[30] in 1996 and its unique tricarbocyclic skeleton attracted our attention. The bifunctional reagent 4-chloro-2-trimethylstannylbut-1-ene[31] (**32**) has been shown to serve as the synthetic

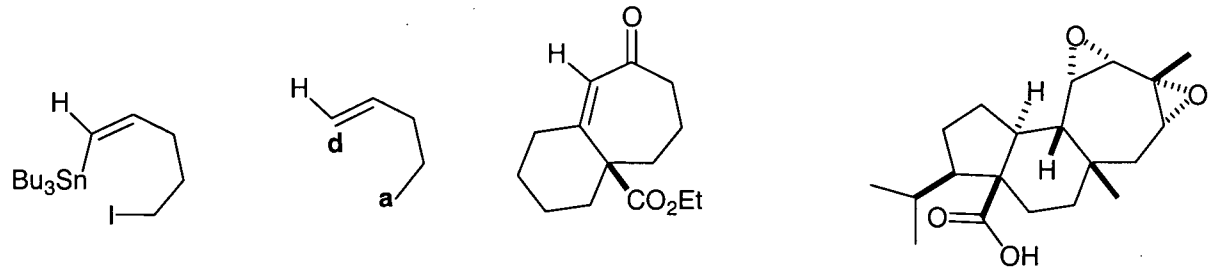
equivalent to the but-1-ene d^2,a^4-synthon (**33**) in a cyclization sequence leading to bicycle ***rac*-34**.[32] The structural similarity between kelsoene (**35**) and bicycle **34** suggested that an expedient total synthesis of the natural product could be achieved, thus showcasing the utility of bifunctional reagent **32**.



32 **33** ***rac*-34** **(+)-kelsoene (35)**

Figure 1.6: Rationale for a total synthesis of kelsoene (35)

The mulinane class of natural products comprises 12 members all having the carbocyclic framework embedded in isomulinic acid[33] (**39**, **Figure 1.7**). A recently developed cycloheptane annulation sequence[34] based on the use of the bifunctional reagent *cis*-5-iodo-1-tributylstannylpent-1-ene (**36**) provides expedient access to bicyclic systems such as compound **38**. In this context reagent **36** may be viewed as the synthetic equivalent of the pent-1-ene d^1,a^5-synthon (**37**). It was hoped that this method would be part of a successful strategy leading to the synthesis of a number of mulinane natural products.



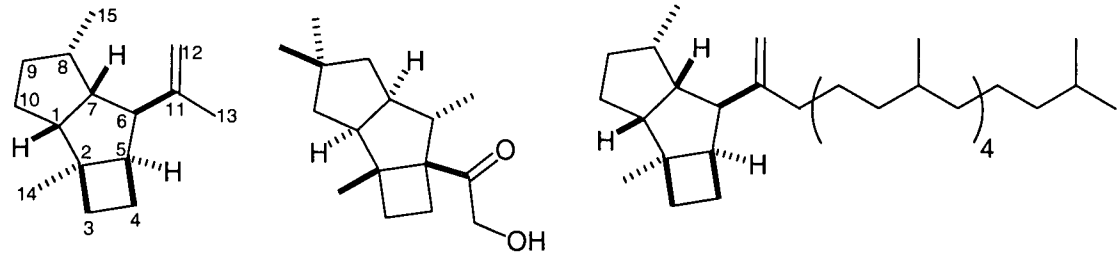
36 **37** **38** **(-)-isomulinic acid (39)**

Figure 1.7: Rationale for a total synthesis of isomulinic acid (39)

2. Total Synthesis of (±)-Kelsoene

2.1 Introduction

In 1996 Wright *et al.* reported the isolation of the novel sesquiterpenoid (+)-kelsoene (**35**) from the dichloromethane extracts of *Cymbastella hooperi*, a marine sponge collected from the Kelso reef, Great Barrier Reef, Australia.[30] In this initial report the authors noted that, at the time of its isolation, the 6-isopropenyl-2,8-dimethyltricyclo[5.3.0.$0^{2,5}$]decane[35] kelsoane carbon skeleton had no precedent in the natural products literature, and provided only a partial assignment of its relative configuration. Indeed, only a single natural product, sulcatine G[36] (**40**), was known to possess the tricyclo[5.3.0.$0^{2,5}$]decane carbocyclic system. The following year the same group showed that kelsoene possesses the relative configuration depicted in **35**.[37] In 1997 it was reported that this "most unusual carbocyclic skeleton" is shared by the tetraterpenoid poduran (**41**),[38] which was isolated from the springtail *Podura aquatica*. Kelsoene has been subsequently isolated from the liverworts *Ptychanthus striatus,*[39,40] *Tritomaria quinquedentata,*[41] and *Calipogeia muelleriana*[42] (**Figure 2.1**).



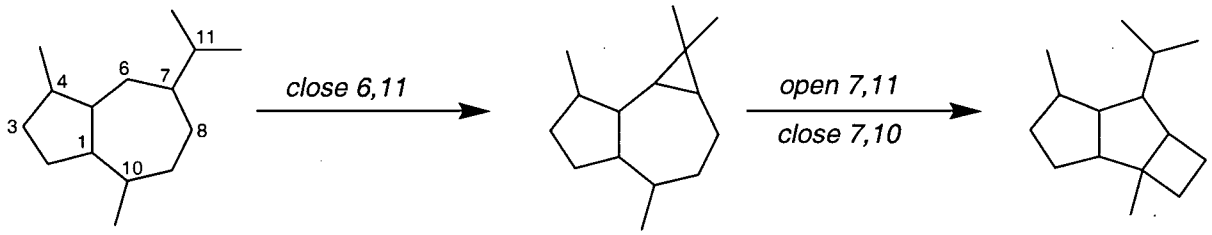
(+)-kelsoene (35) **sulcatine G (40)** **poduran (41)**

Figure 2.1: kelsoene and related natural products

Due to its unique and unprecedented structure, and in order to determine its absolute configuration, kelsoene has been the subject of biosynthetic,[39,43] spectroscopic,[44] and synthetic studies.[45-50]

2.2 Biogenesis

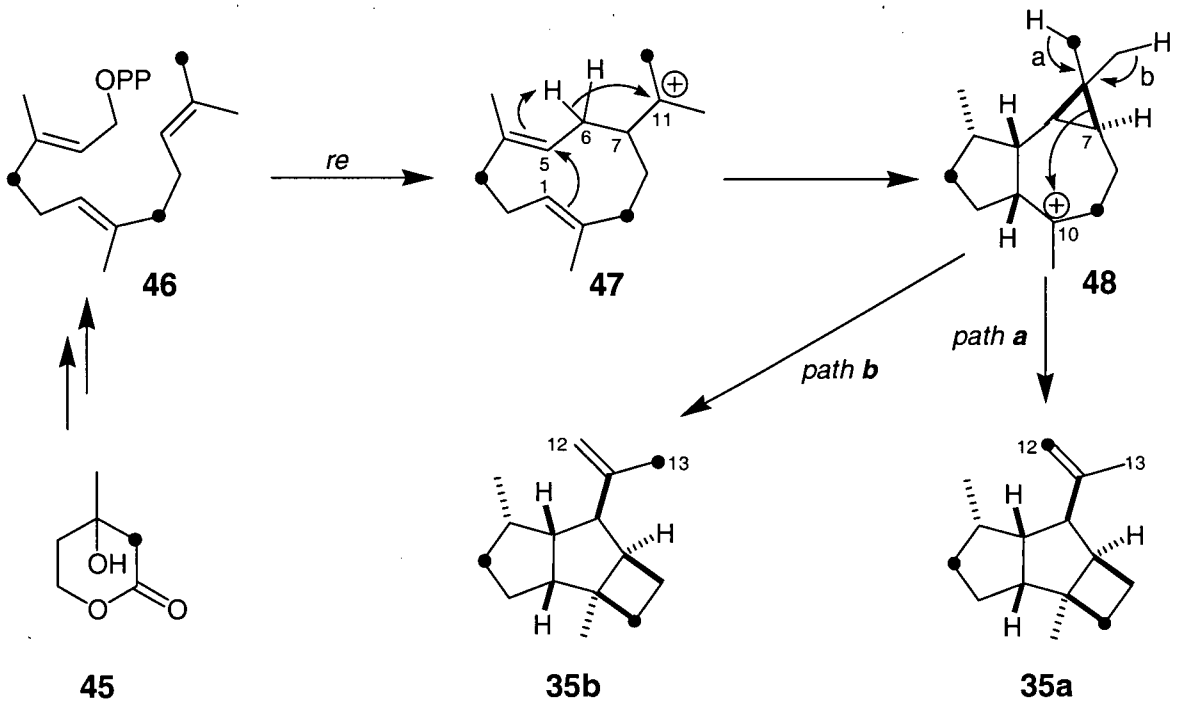
Shortly after their initial report König and Wright proposed a biosynthetic path to kelsoene.[37] They reasoned that kelsoene might be derived from a guaiane skeleton (**42**), which must first undergo a ring closure between C-6 and C-11 to generate an *allo*-aromadendrane species (**43**). The bond between C-7 and C-11 is then broken, and a new bond between C-7 and C-10 is formed to generate the kelsoane skeleton (**44**, **Scheme 2.1**).



42 **43** **44**

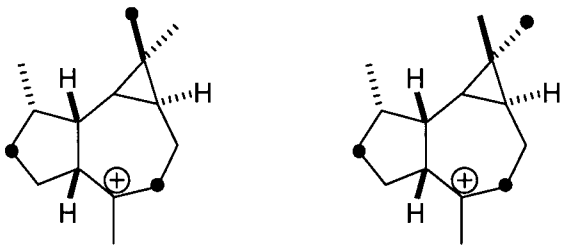
Scheme 2.1: König and Wright's proposed biosynthesis of kelsoene[37]

A year later Nabeta *et al.*[39,43] outlined a more explicit biosynthetic path to kelsoene from farnesyl diphosphate (**46**, **Scheme 2.2**). In their study, cells of the liverwort *Ptychanthus striatus* were incubated with [2-$^2H_2$]-, [5-$^2H_2$]-, and [2-^{13}C]-potassium mevalonate (**45**), and the labeling patterns of the biosynthetically labeled ^{2}H- or ^{13}C-kelsoene were determined by GLC-MS, ^{2}H- and ^{13}C-NMR analyses. Thus, initial cyclization of farnesyl diphosphate (**46**) from the *re*-face forms the (–)-germacradienyl cation (**47**). This cation then cyclizes stereospecifically between C-1 and C-5, and between C-6 and C-11 to furnish the (+)-*allo*-aromadendranyl cation (**48**). Finally, the cyclopropane ring is cleaved and a ring closing reaction between C-7 and C-10 ensues, with concomitant loss of a proton, to afford kelsoene.



Scheme 2.2: Nabeta's proposed biosynthesis of kelsoene[39,43]

Curiously, Nabeta *et al.* observed randomization of the ^{13}C label between C-12 and C-13 (**Scheme 2.2**). They proposed two possible explanations for the observed randomization. The first involves an "equivalent loss of a proton from the *gem*-dimethyls". Thus, loss of a proton through path ***a*** would yield kelsoene labeled at the terminal sp^2 carbon of the isopropenyl moiety. Alternatively, loss of a proton through path ***b*** would place the ^{13}C label at the sp^3 carbon of the isopropenyl moiety of kelsoene. A second and more likely explanation invokes free rotation about the C-7 and C-11 bond in **47**. Thus a stereospecific ring closure between C-11 and C-6 may occur when the ^{13}C label is on the β-face of germacradienyl cation to afford **48a**. Alternatively, the same stereospecific ring closure may occur when the ^{13}C label is on the α-face of the germacradienyl cation to afford **48b** (**Figure 2.2**). A stereospecific elimination-cyclization sequence would lead from cations **48a** and **48b** to **35a** and **35b**.

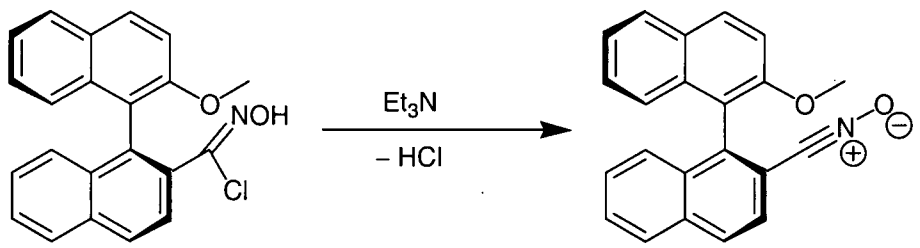


48a **48b**

Figure 2.2: Differentially labeled *allo*-aromadendranyl cations[39,43]

2.3 Spectroscopic determination of the absolute configuration of (+)-kelsoene.

In 1998 Fukui *et al.* disclosed a new method for the recognition of chiral organic compounds by NMR spectroscopy.[51] Their research in this field was prompted by the lack of chiral derivitazing agents for chiral alkenes. This new method relies on the well known dipolar cycloaddition of nitrile oxides to electron rich alkenes. Thus, when the axially chiral reagent 2'-methoxy-1,1'-binaphthalen-2-carbohydroximoyl chloride ((a*S*)-MBBC, **49**) is treated with a tertiary amine, a reactive chiral nitrile oxide (**50**) is generated (**Scheme 2.3**).

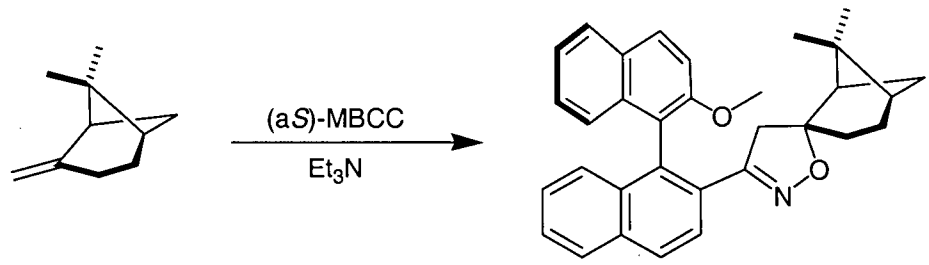


(a*S*)-MBCC (49) **50**

Scheme 2.3: Generation of an axially-chiral nitrile oxide[51]

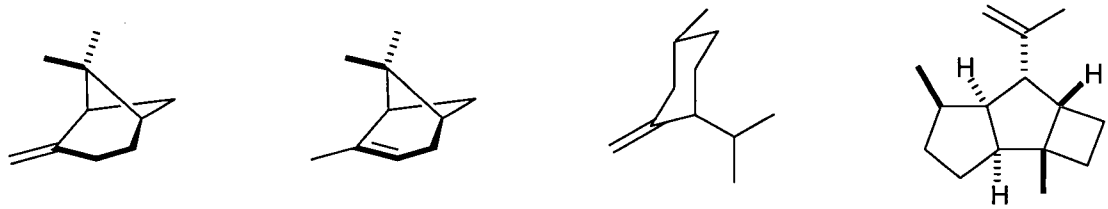
In principle, this chiral nitrile oxide can form a covalent adduct with a chiral olefin of undetermined absolute configuration (**Scheme 2.4**). The relative stereochemistry of the adduct can then be assigned based on NMR spectroscopic data. Thus, since the

absolute stereochemistry of the chiral reagent is known, the absolute configuration of the alkene in question can be assigned. This hypothesis was substantiated by a series of experiments carried out on adducts formed between nitrile oxide **50** and (–)-β-pinene (**51**), (–)-α-pinene (**53**) and an olefin derived from (–)-menthone (**54**) (**Figure 2.3**).



51 **52**

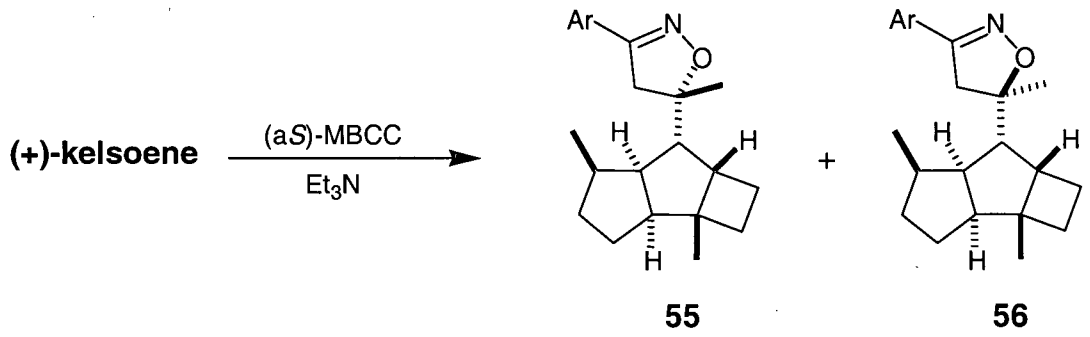
Scheme 2.4: Derivatization of (–)-β-pinene with (a*S*)-MBCC (49)[51]



51 **53** **54** ***ent*-35**

Figure 2.3: Chiral alkenes derivatized with (aS)-MBCC (49)[51]

In view of the fact that kelsoene possesses an olefin as its single functional group, Nabeta *et al.* decided to apply Fukui's method to determine its absolute configuration.[44] Thus, treatment of a mixture of (+)-kelsoene and the axially chiral reagent (a*S*)-MBBC (**49**) with triethylamine for 14 days provided a mixture of covalent adducts **55** and **56** in a 62:38 ratio and 10% overall yield (**Scheme 2.5**). Careful analysis of the spectroscopic data derived from a substance believed to be **55** led these authors to (incorrectly) assign the absolute configuration of (+)-kelsoene as that depicted in ***ent*-35** (**Figure 2.3**).



55 56

Scheme 2.5: Derivatization of (+)-kelsoene with (a*S*)-MBCC[44]

In retrospect, the fact that two covalent adducts were formed in a nearly 3:2 ratio should have cast doubts on the conclusions reached by Nabeta *et al.* Indeed, careful inspection of the three substrates used in Fukui's study (**51**, **53** and **54**) reveals that in all cases at least one of the sp^2 centers resides in the carbocyclic core of the molecule. Furthermore, based on the structure of these substances, addition of the nitrile oxide is expected to occur with a high degree of facial selectivity. Clearly, neither of these conditions is met in the spectroscopic study of (+)-kelsoene.

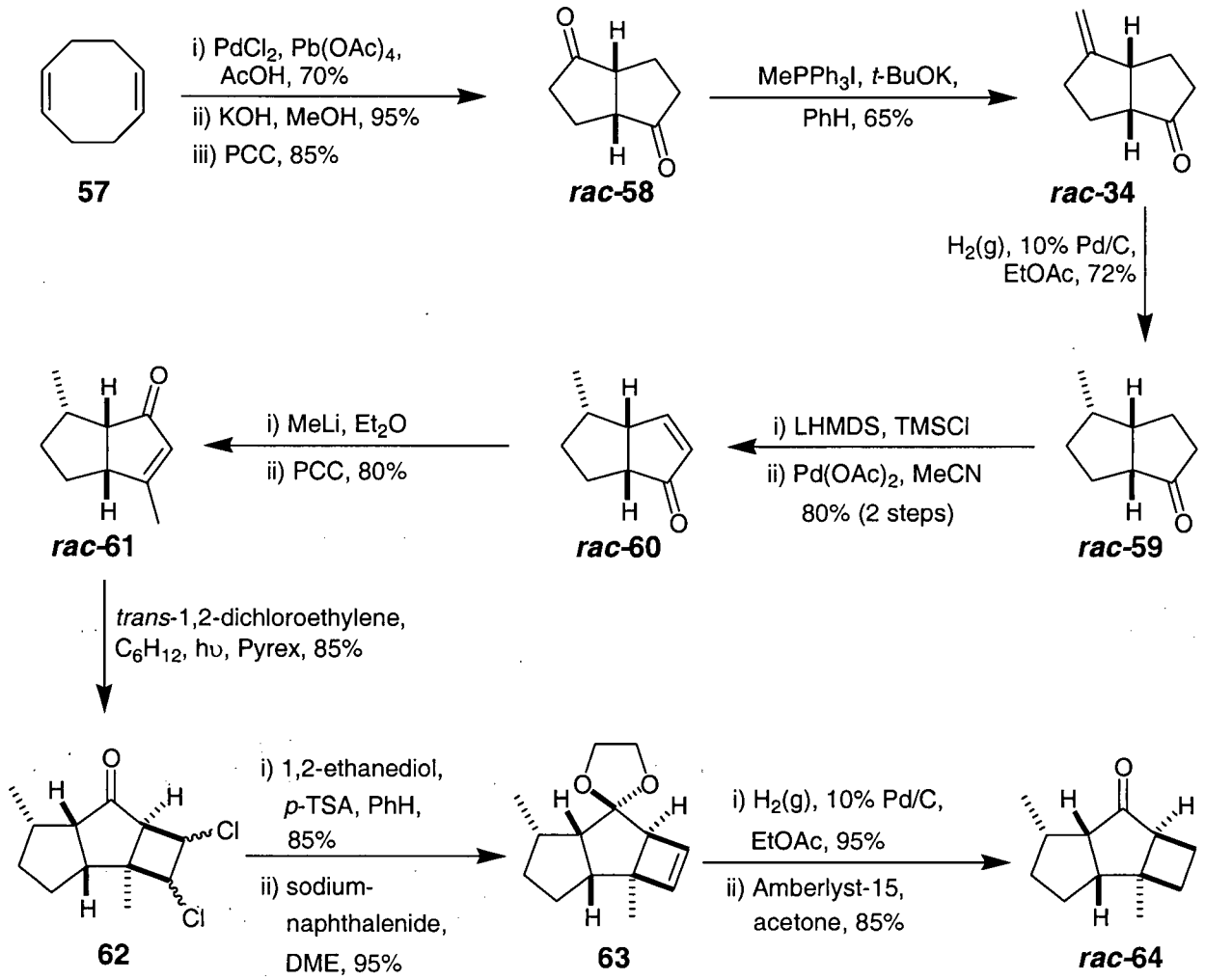
2.4 Reported Syntheses of kelsoene

2.4.1 Total synthesis of (±)-kelsoene by Mehta and Srinivas.[45,46]

It is evident that the unusual nature of the kelsoane skeleton, the presence of a single functional group and its six contiguous carbon chirality centers combine to make kelsoene a significant synthetic challenge. The first foray into a total synthesis of this natural product was reported by Mehta and Srinivas in 1999.[45] Their synthetic approach was clearly influenced by the recognition that quick access to the diquinane core of kelsoene would facilitate the construction of the natural product in an expedient fashion.

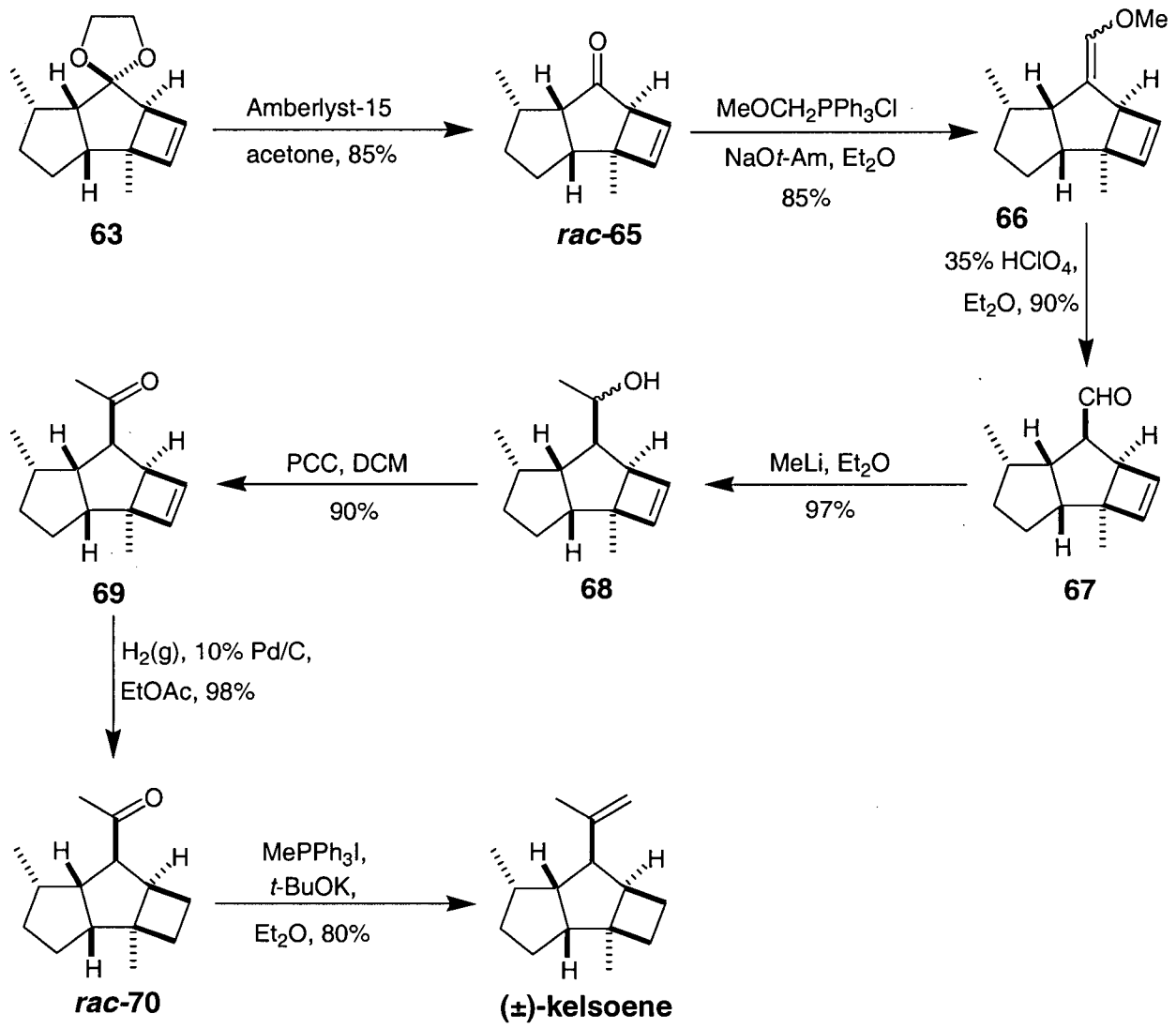
The sequence begins with the preparation of the C_2-symmetric diketone (***rac*-58**) from commercially available 1,5-cyclooctadiene (**57**) using the method described by Henry *et al.*[52] (**Scheme 2.6**). Wittig mono-methylenation of this diketone provided alkenone ***rac*-34** in good yield. Hydrogenation of the exocyclic olefin under heterogeneous conditions proceeded, as expected, from the convex surface of the bicycle with a good degree of facial selectivity (60% diastereomeric excess) and in excellent yield. The bicyclic ketone (***rac*-59**) was dehydrogenated using the method established by Saegusa,[53] and the resulting enone (***rac*-60**) was alkylated with methyllithium to generate a tertiary allylic alcohol. This unstable intermediate was treated with pyridinium chlorochromate to furnish the desired enone (***rac*-61**) in good yield. At this stage the authors elected to construct the four membered ring of kelsoene using a [2+2]-photocycloaddition between enone ***rac*-61** and *trans*-1,2-dichloroethylene. Protection of the carbonyl function of the resultant tricycle (**62**) was necessary for the reductive dehalogenation of the four membered ring to proceed efficiently. Finally, hydrogenation of the cyclobutene moiety in **63** followed by deprotection of the carbonyl group provided the desired tricyclic ketone ***rac*-64**.

Having achieved a synthesis of the tricarbocyclic core of kelsoene, Mehta and Srinivas attempted the installation of the isopropenyl moiety in the natural product. Unfortunately, ketone ***rac*-64** proved to be "extremely refractory" towards various reagents, a behaviour which was attributed to the sterically encumbered environment around the carbonyl group.



Scheme 2.6: Construction of ketone *rac*-64 by Mehta and Srinivas[45]

Undeterred by these results, the authors revised their strategy towards the synthesis of kelsoene.[46] In order to enhance the reactivity of ketone ***rac*-64** it became necessary to alleviate the steric congestion around its carbonyl group. It was postulated that simply transforming ketal **63** into ketone ***rac*-65** would afford a substrate that could be elaborated to the natural product (**Scheme 2.7**). Indeed, ketone ***rac*-65** could be converted into methyl enol ether **66** in excellent yield using a Wittig olefination protocol. Acid hydrolysis of this substrate provided a single aldehyde (**67**) as the major product. This aldehyde was easily alkylated with methyllithium to provide a mixture of epimeric alcohols (**68**) which could be oxidized to the corresponding ketone (**69**) in excellent yield. This material was readily hydrogenated, and the resulting ketone (***rac*-70**) was converted to (±)-kelsoene through a Wittig methylenation.

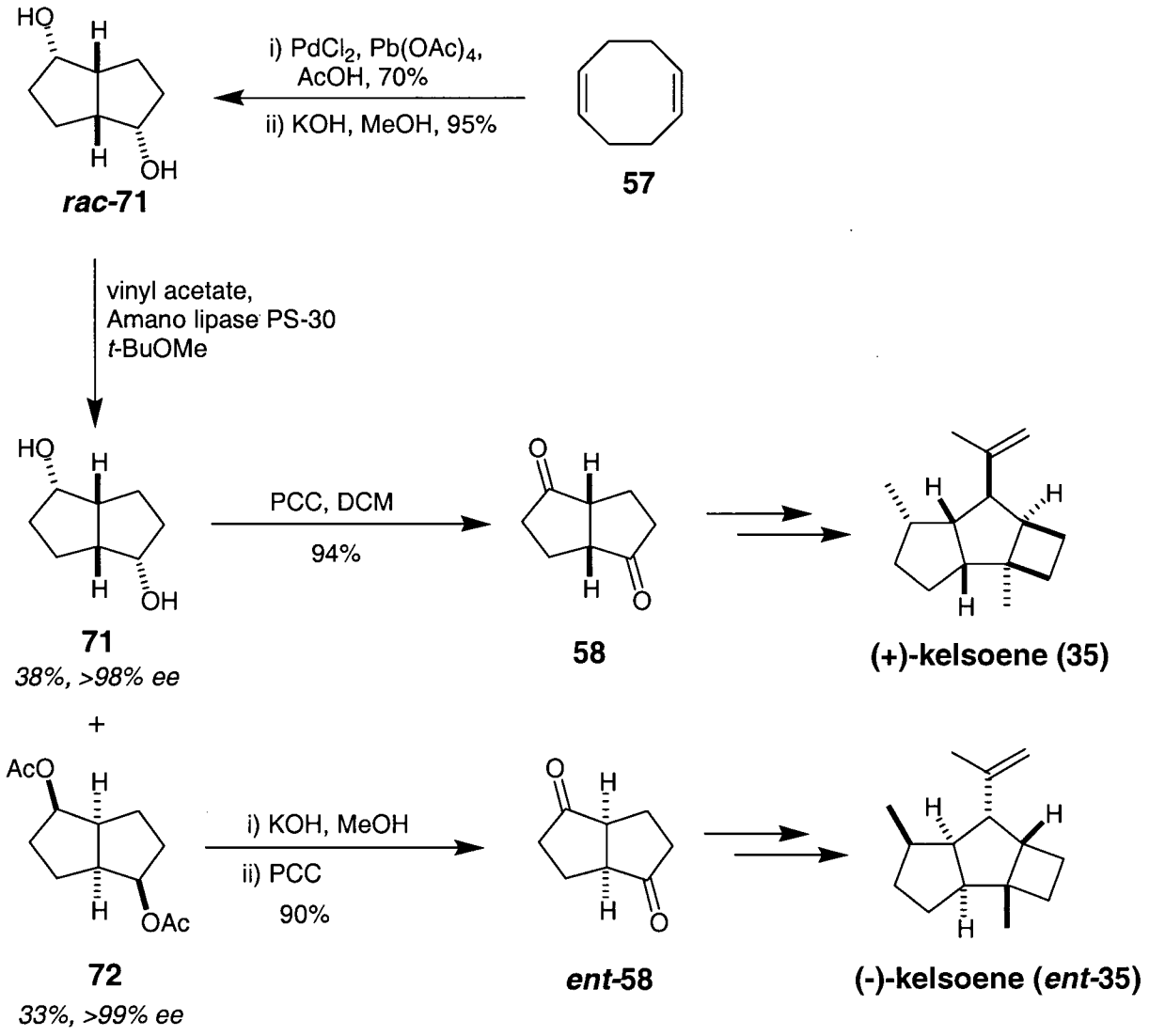


Scheme 2.7: Total synthesis of (±)-kelsoene by Mehta and Srinivas[46]

2.4.2 Enantioselective total synthesis of (+)-kelsoene and (-)-kelsoene by Mehta and Srinivas. Determination of the absolute configuration of (+)-kelsoene.[47]

Having achieved a total synthesis of (±)-kelsoene, Mehta and Srinivas[47] set out to determine the absolute configuration of this natural product using the synthetic sequence previously developed. To accomplish this, diketones **58** and ***ent*-58** were required with a high degree of enantiomeric purity. Thus the bicyclic diol ***rac*-71** was

constructed in racemic form using Henry's procedure[52] (**Scheme 2.8**). A lipase catalyzed kinetic resolution was employed to provide diol **71** and diacetate **72** in good yield and excellent enantiomeric excess. Diol **71** was readily oxidized to diketone **58**, while diacetate **72** was first hydrolyzed under basic conditions to the corresponding diol and subsequently oxidized to diketone ***ent*-58**. The absolute configuration of the chiral diones **58** and ***ent*-58** had been previously determined.



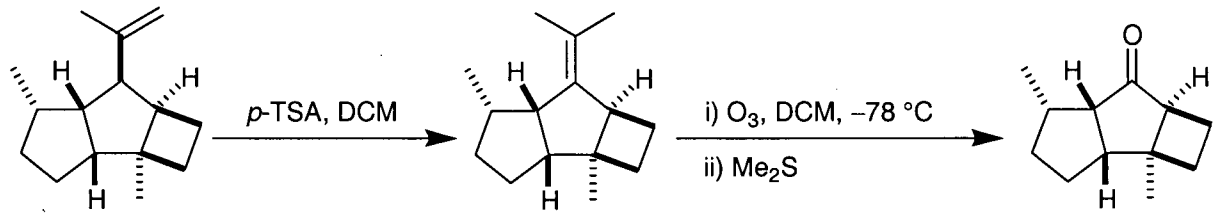
Scheme 2.8: Enantioselective total synthesis of (+)-kelsoene and (-)-kelsoene by Mehta and Srinivas [47]

Diketone **58** was subjected to the 15-step synthetic sequence used for the synthesis (±)-kelsoene and provided (+)-kelsoene (**35**) as determined by a measurement of its optical rotation. In a similar fashion, diketone ***ent*-58** provided (–)-kelsoene (***ent*-35**). Thus the absolute configuration of naturally occurring (+)-kelsoene could be unambiguously assigned as that depicted in **35**.

2.4.3 Enantiospecific total synthesis of (-)-kelsoene by Schulz and coworkers. Determination of the absolute configuration of (+)-kelsoene.[48]

A second synthetic study aimed at determining the absolute configuration of (+)-kelsoene was carried out by Schulz and coworkers.[48] Their approach relied on the chemical degradation of naturally occurring (+)-kelsoene and on the enantiospecific synthesis of (–)-kelsoene from (*R*)-(+)-pulegone.

It was reasoned that naturally occurring (+)-kelsoene could be degraded to a tricyclic intermediate which could be constructed in enantiomerically pure form from (*R*)-(+)-pulegone. Chiral GC analysis of these materials would then allow the absolute configuration of (+)-kelsoene to be determined.



(+)-kelsoene (35) **73** **64**

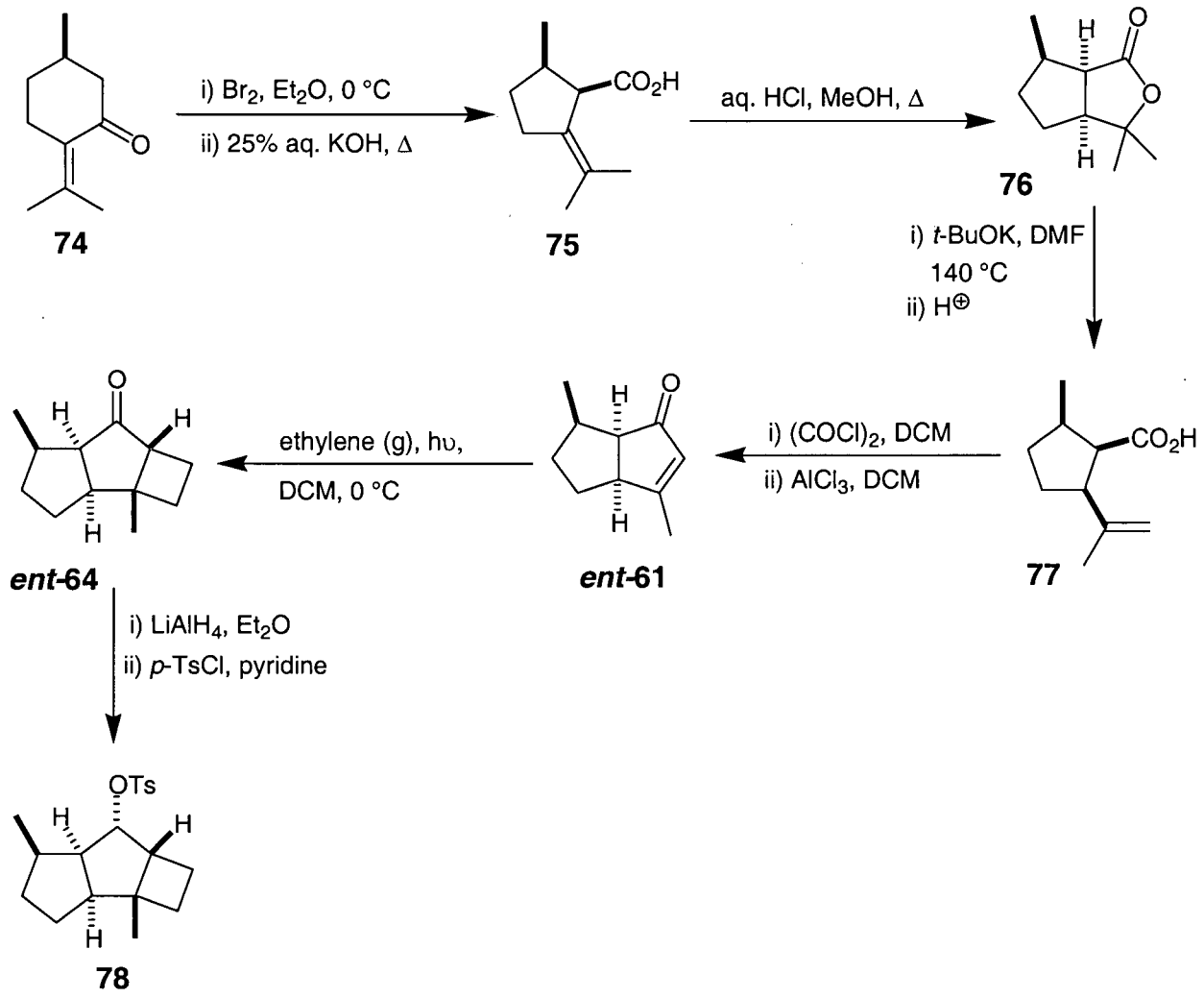
Scheme 2.9: Chemical degradation of (+)-kelsoene[48]

The chemical degradation of (+)-kelsoene was carried out in a straightforward manner (**Scheme 2.9**). Thus, treatment of the natural product with *p*-toluenesulfonic acid isomerized the olefin to its more stable isomer (**73**). The double bond was then cleaved with ozone to provide the expected tricyclic ketone (**64**).

At this stage it was necessary to construct tricyclic ketone **64** (or its enantiomer) in enantiomerically rich form. Thus (R)-(+)-pulegone (**74**) was transformed into a mixture of *cis*- and *trans*-pulegonic acids using a bromination reaction followed by a Favorskii rearrangement (**Scheme 2.10**). These diastereomers were chromatographically separated and the *cis*-isomer (**75**) was converted to the bicyclic lactone **76** under acidic conditions. This material was subjected to a base mediated ring opening reaction, which served to establish the isopropenyl moiety. Carboxylic acid **77** was transformed to the corresponding acid chloride, and this material was converted into the necessary bicyclic ketone (***ent*-61**) in the presence of a strong Lewis acid. The four-membered ring was installed in a manner similar to that used by Mehta and Srinivas. Thus irradiation of a mixture of ethylene gas and bicyclic enone ***ent*-61** provided the requisite tricyclic ketone (***ent*-64**).

Chiral GC analysis of compounds **64** and ***ent*-64** revealed that these two ketones exhibited different retention times and, therefore, have an enantiomeric relationship. Thus, being confident of the absolute configuration of the tricyclic ketone derived from (R)-(+)-pulegone, it could be deduced that the absolute configuration of naturally occurring (+)-kelsoene is that depicted in **35**.

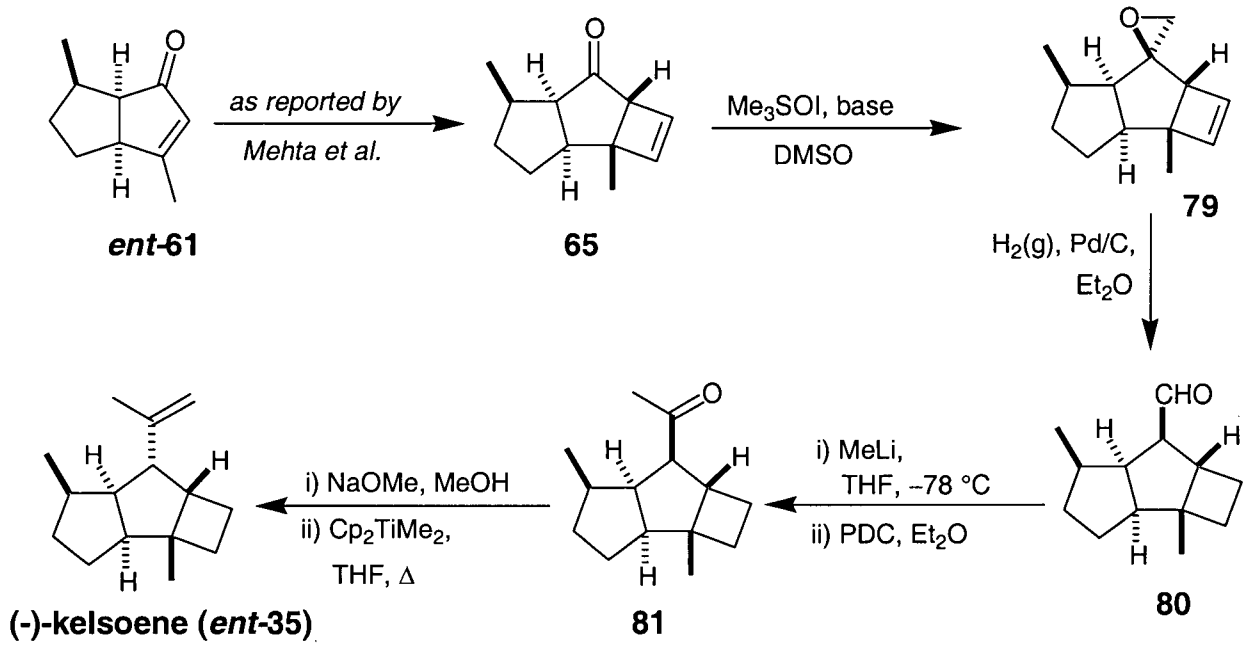
Further support for this assignment was provided by an X-ray analysis on *p*-toluenesulfonate **78**. This material was prepared by hydride reduction of ketone ***ent*-64**, followed by a tosylation reaction (**Scheme 2.10**).



Scheme 2.10: Construction of *ent*-64 from (R)-(+)-pulegone[48]

Finally, (–)-kelsoene (***ent*-35**) was prepared from bicyclic ketone ***ent*-61**. The latter substance was elaborated to tricyclic alkenone **65** using the protocol devised by Mehta and Srinivas[45,46] (**Scheme 2.11**). Alkenone **65** was treated with the ylide derived from trimethylsulfoxonium iodide to generate epoxide **79**. Hydrogenation of the cyclobutene moiety in **79** was accompanied by the rearrangement of the epoxide to the corresponding aldehyde to furnish compound **80**. This aldehyde was alkylated with methyllithium, and the resulting mixture of secondary alcohols was oxidized to the corresponding ketone (**81**). Finally, this ketone was equilibrated to its more thermodynamically stable epimer and subsequently converted to (–)-kelsoene (***ent*-35**) using the methylenation method described by Petasis.[54] An optical rotation

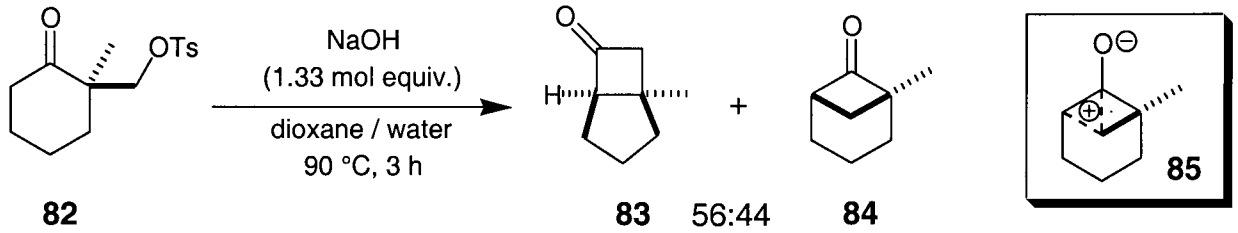
measurement verified that this material is indeed enantiomeric to naturally occurring (+)-kelsoene (**35**).



Scheme 2.11: Enantiospecific total synthesis of (-)-kelsoene from (R)-(+)-pulegone[48]

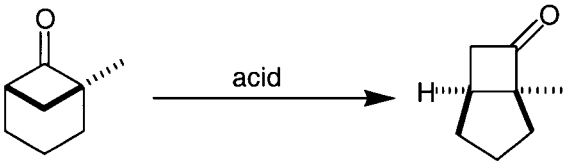
2.4.4 Total Synthesis of (±)-kelsoene by Zhang and Koreeda.[50]

This synthesis relies on two key transformations to construct the tricyclic framework of kelsoene.[50] It is known that γ-keto-*p*-toluenesulfonates undergo a stereospecific homoallyl rearrangement, commonly referred to as the homo-Favorskii rearrangement. For example, treatment of 2-methyl-2-tosyloxymethylcyclohexane (**82**) with hot NaOH provides bicyclo[3.2.0]heptanone **83** through the homo-Favorskii rearrangement (**Scheme 2.12**). The isomeric bicyclo[3.1.1]heptanone **84** is obtained as the major side product in this reaction. The occurrence of these two isomers indicates that the reaction likely proceeds through the intermediacy of the non-classical zwitterion **85**.



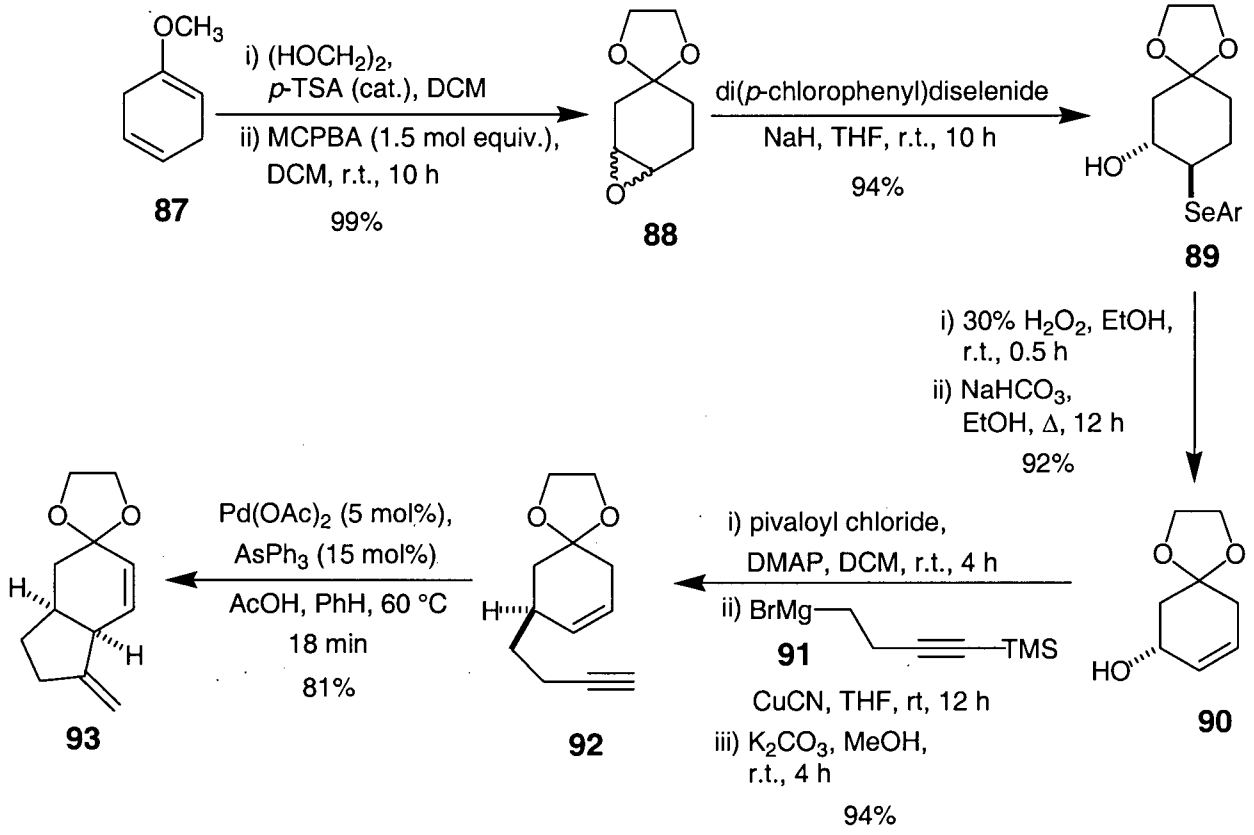
Scheme 2.12: Homo-Favorskii rearrangement of γ-keto-*p*-toluenesulfonate 82[50]

Interestingly, bicyclo[3.1.1]heptanones are readily rearranged to the isomeric bicyclo[3.2.0]heptanones by treatment with mild acid (**Scheme 2.13**). It is thought that this rearrangement is driven by the relatively higher strain energy of bicyclo[3.1.1]heptanones.[187,188] Thus, the two constitutional isomers arising from the homo-Favorskii rearrangement of γ-keto-*p*-toluenesulfonates converge to the more stable bicyclo[3.2.0]heptanone products upon treatment with mild acid.



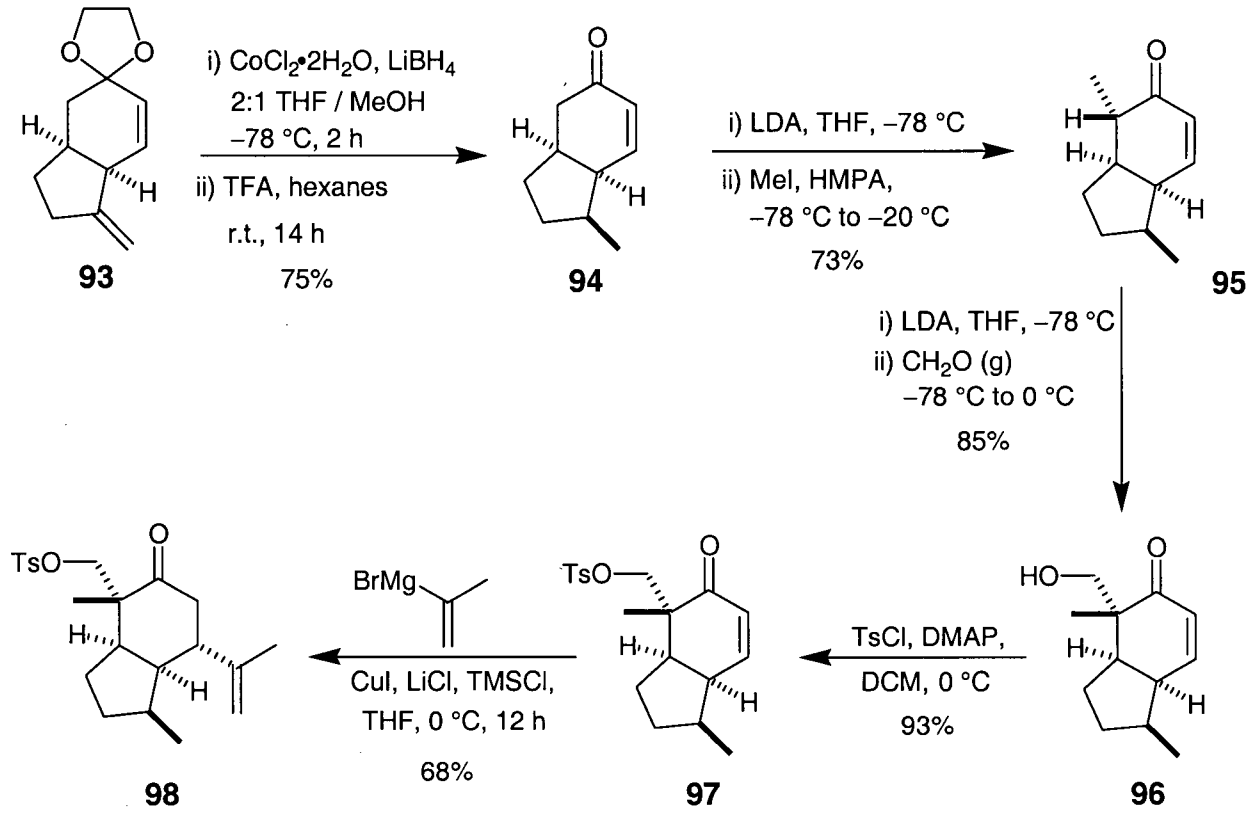
Scheme 2.13: Acid catalyzed isomerization of bicyclo[3.1.1]heptanone to bicyclo[3.2.0]heptanone[50]

The synthesis begins with the conversion of the enol ether moiety of 2,5-dihydroanisole (**87**) to the corresponding ethylene ketal (**Scheme 2.14**). The remaining double bond was then oxidized with MCPBA to provide a mixture of diastereomeric epoxides (**88**). The oxirane was opened with sodium *p*-chlorophenylselenide and the resulting adduct (**89**) was oxidized to the corresponding selenoxide. Thermolysis of this material afforded the desired allylic alcohol (**90**). The cyanocuprate derived from copper(I) cyanide and Grignard reagent **91** reacted smoothly with the pivaloate derived from compound **90**, and desilylation of the resulting adduct furnished enyne **92**. A palladium catalyzed enyne cyclization afforded the desired bicyclic carbocycle **93**.



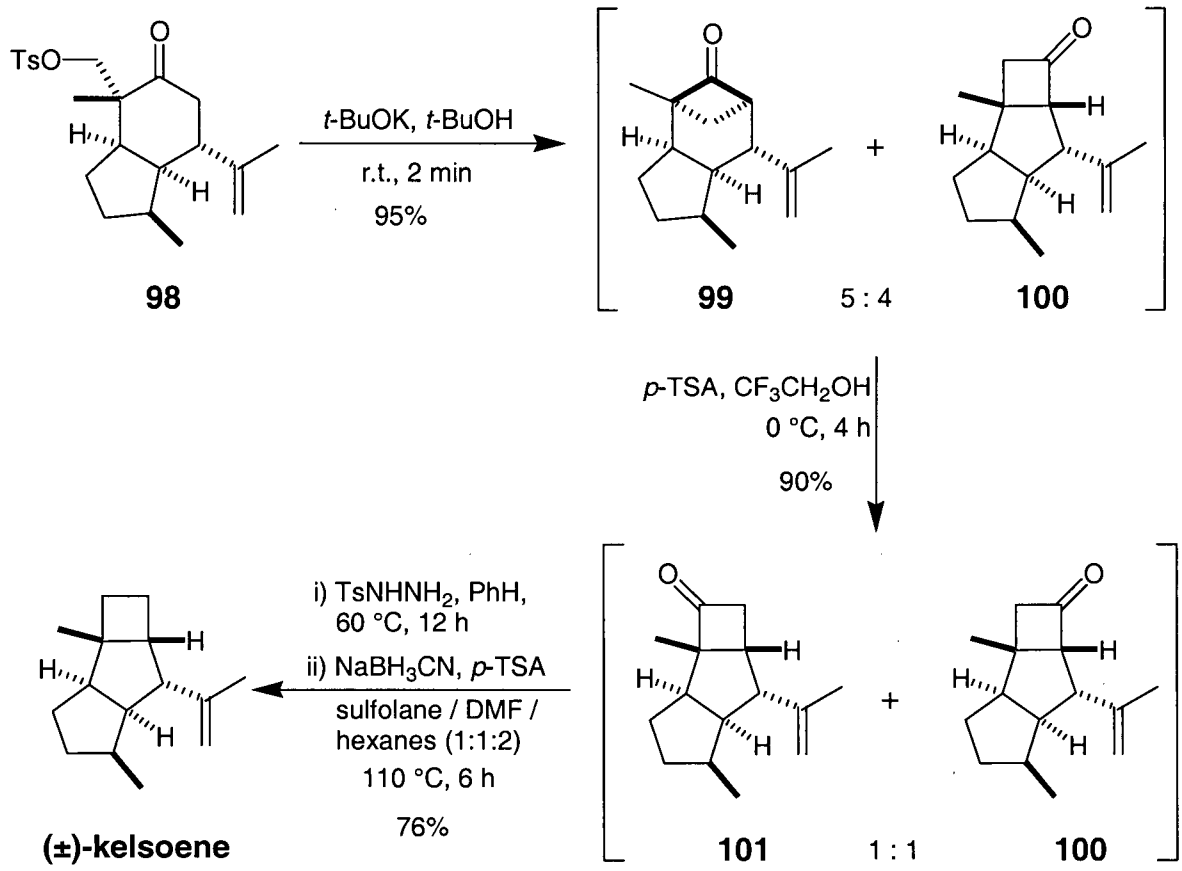
Scheme 2.14: Preparation of enyne 93[50]

The reduction of the exocyclic double bond in **93** was accomplished through the use of $CoCl_2/LiBH_4$ with a high degree of diastereoselectivity (**Scheme 2.15**). At this stage, the ketal moiety was converted to the corresponding ketone to furnish enone **94**. Methylation of compound **94**, followed by hydroxymethylation of the resulting material provided enone **96**. As expected, both alkylation steps occurred from the convex face of the bicyclic system. The hydroxyl group of enone **96** was then converted to the corresponding tosylate in high yield. Conjugate addition of an isopropenyl group to the convex face of enone **97** generated the γ-keto-*p*-toluenesulfonate (**98**) required for the crucial homo-Favorskii rearrangement.



Scheme 2.15: Preparation of γ-keto-*p*-toluenesulfonate 98[50]

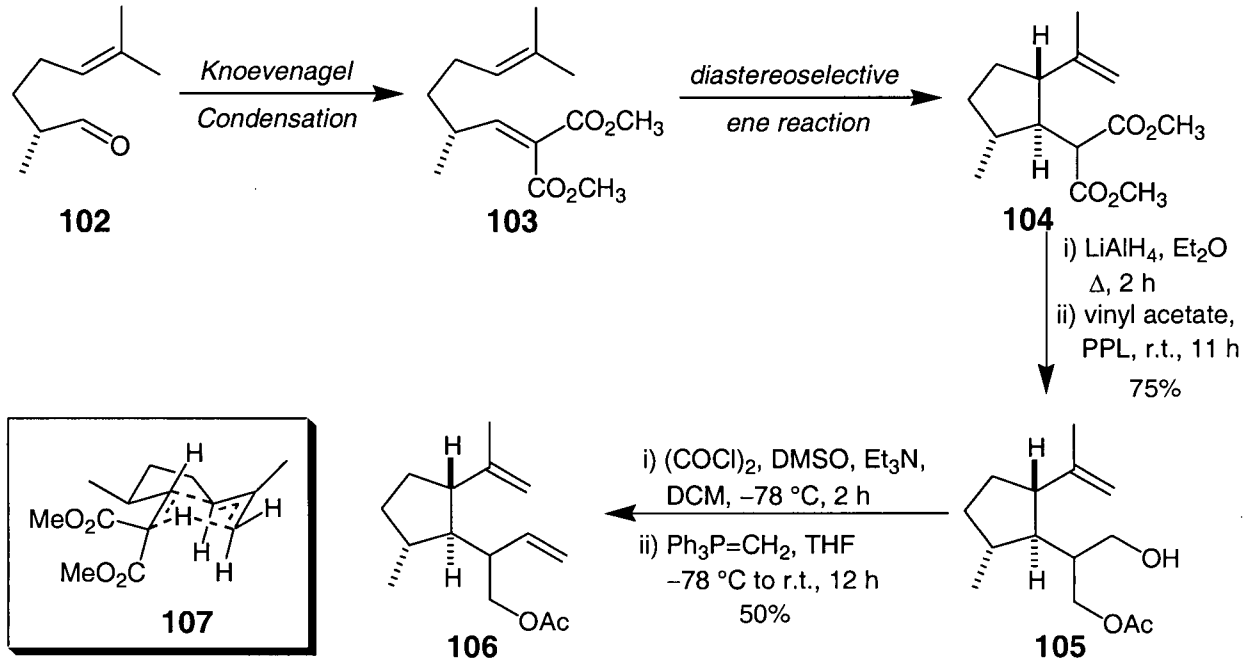
Treatment of keto-*p*-toluenesulfonate **98** with an excess of *t*-BuOK provided, as expected, a mixture of cyclobutanone products **99** and **100** (**Scheme 2.16**). Although these materials could be easily separated, the mixture was treated with mild acid in order to isomerize cyclobutanone **99** to its more stable constitutional isomer (**101**). Cyclobutanones **100** and **101** were converted to the corresponding tosylhydrazones, and these were subsequently reduced to furnish (±)-kelsoene in 76% yield over the two steps.[50]



Scheme 2.16: Completion of the synthesis of (±)-kelsoene by Zhang and Koreeda[50]

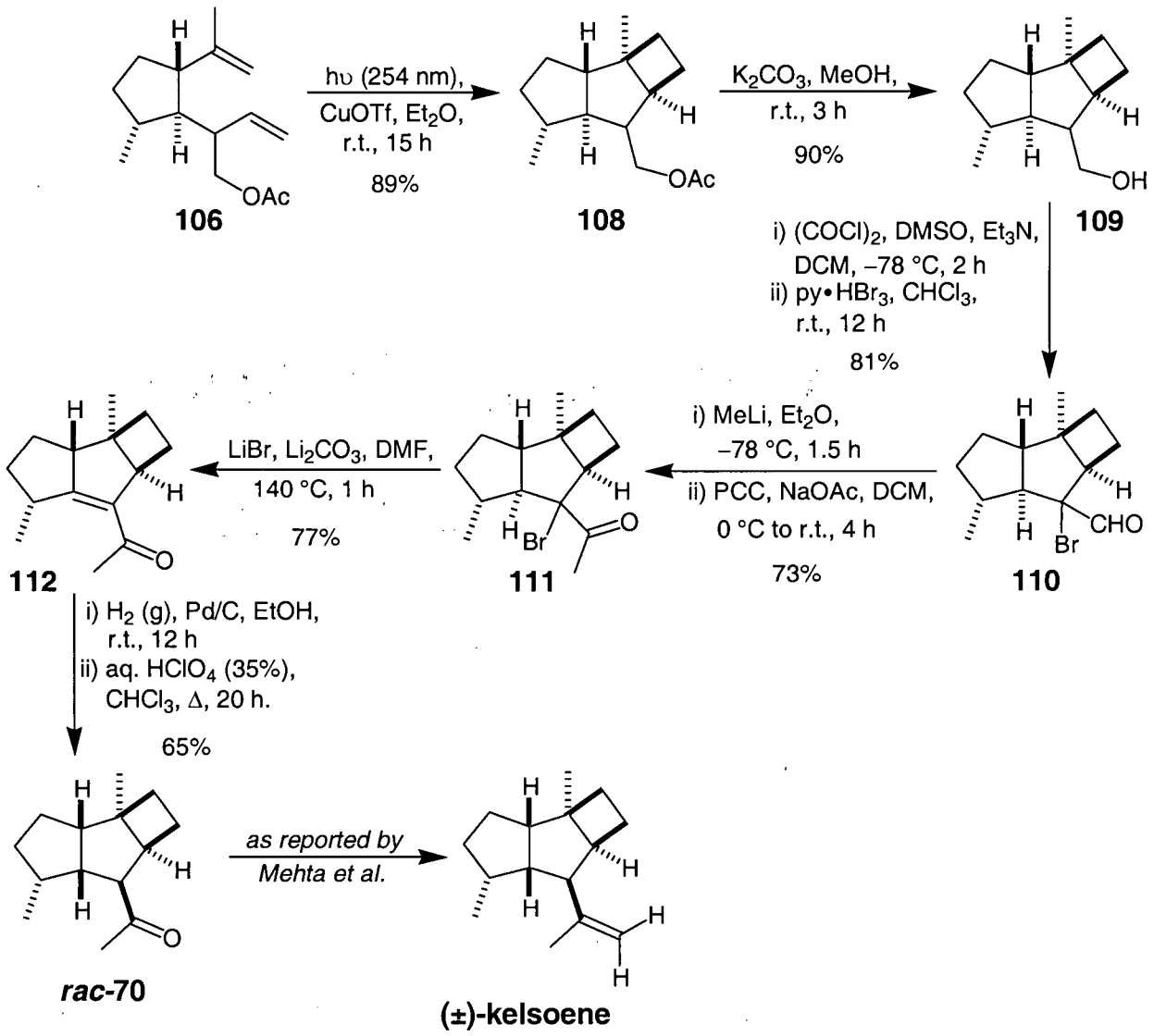
2.4.5 Total Synthesis of (±)-kelsoene by Bach and Spiegel[49]

The most recently reported synthesis of (±)-kelsoene[49] differs significantly in approach from those reported earlier, including the work described in this thesis. The synthesis begins with the preparation of the 1,6-diene **103** through a Knoevenagel condensation of dimethyl malonate with aldehyde **102** (**Scheme 2.17**). The highly diastereoselective intramolecular ene reaction of **103** leading to the cyclopentane **104** is thought to occur through a chair-like transition state as depicted in **107**.[55] Reduction of diester **104**, followed by a porcine pancreatic lipase catalyzed acetylation of the resulting diol provides compound **105** as a mixture of diastereomers. The free alcohol is oxidized to the aldehyde and subsequently converted to the corresponding olefin (**106**) using a Wittig protocol.



Scheme 2.17: Synthesis of 1,6-diene 106[49]

The diastereomeric mixture of substances **106** was subjected to photochemical [2+2]-cycloaddition conditions[56] and furnished the tricarbocyclic compounds **108** (**Scheme 2.18**). As expected, the rings embedded in this key intermediate exist in a *trans-anti-cis* arrangement. Methanolysis of ester **108** to alcohol **109** was followed by Swern oxidation to the corresponding aldehyde. This material provided α-bromoaldehyde **110** as a single diastereomer upon treatment with py•HBr_3,[57] but the relative configuration of the carbon chirality center associated with the aldehyde was not ascertained. Addition of MeLi to α-bromoaldehyde **110** and oxidation of the resulting secondary alcohol furnished α-bromoketone **111**. Elimination of hydrogen bromide from **111** provided the expected conjugated enone **112**. As anticipated, hydrogenation of its double bond provided the requisite *cis-anti-cis* carbocycle with the incorrect relative configuration at the carbon chirality center associated with the acetyl group. Epimerization of this intermediate under acidic conditions to ketone ***rac*-70** and olefination using a Wittig protocol resulted in the synthesis of (±)-kelsoene.



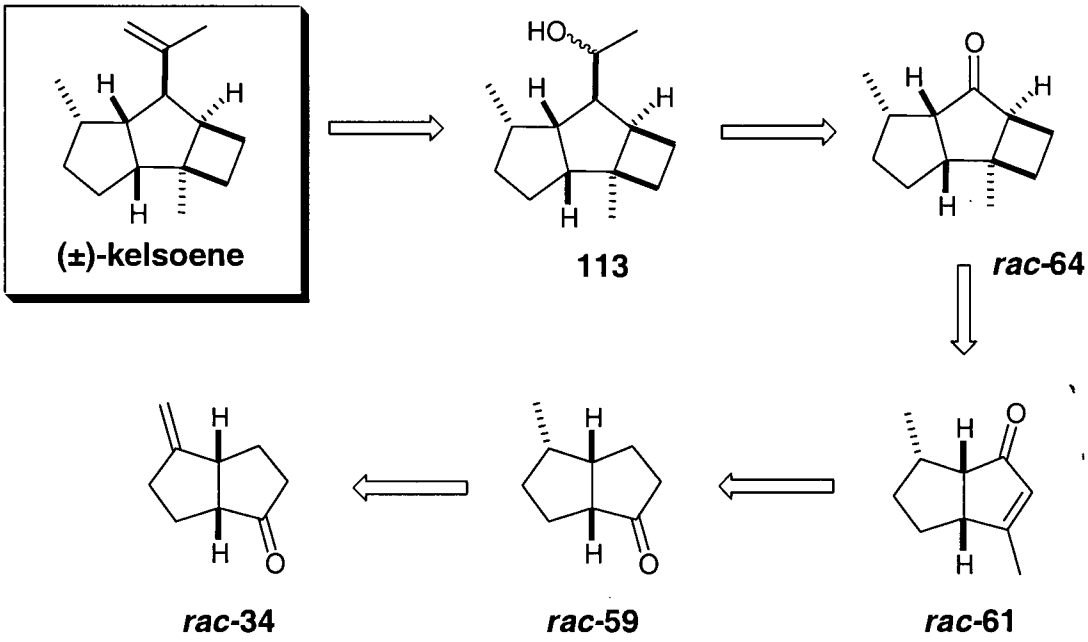
Scheme 2.18: Completion of the synthesis of (±)-kelsoene by Bach and Spiegel[49]

2.5 Total synthesis of (±)-kelsoene

2.5.1 Retrosynthetic analysis

Notwithstanding its low molecular weight, kelsoene represents a significant synthetic challenge. In addition to its unusual tricarbocyclic skeleton, kelsoene possesses six contiguous carbon chirality centers, one of which is quaternary.

The retrosynthetic analysis of kelsoene began with the recognition that a tricarbocyclic ketone such as ***rac*-64**, in which the correct relative configuration of five carbon chirality centers is set, could be elaborated to the natural product (**Scheme 2.19**). This process would entail homologation of the ketone to the corresponding aldehyde, followed by an alkylation to generate the requisite secondary alcohol (**113**). Finally, oxidation of the alcohol to the corresponding ketone, followed by a methylenation reaction would furnish racemic kelsoene. It was expected that the four membered ring in ketone ***rac*-64** could be constructed using a [2+2]-photocycloaddition of a suitable enone such as ***rac*-61** with ethylene, using the protocol devised by Caldwell and coworkers.[58] It was expected that the requisite *cis-anti-cis* relationship in ketone ***rac*-64** would be established through the preferential approach of ethylene from the convex surface of enone ***rac*-61** during the photocycloaddition event.[59] Enone ***rac*-61** could, in principle, be obtained from ketone ***rac*-59** by oxidation to the corresponding enone, followed by 1,2 addition of methyllithium and oxidative rearrangement of the resulting tertiary allylic alcohol. The relative configuration of the methyl group in ketone ***rac*-59** was expected to be established through a preferential hydrogenation of an exocyclic olefin from the convex face of bicyclic ketone ***rac*-34**.

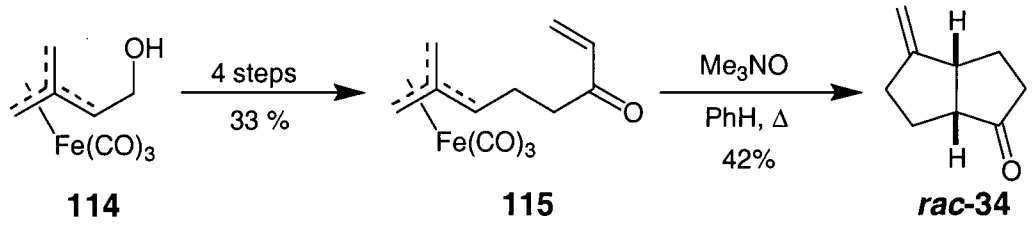


Scheme 2.19: Retrosynthetic analysis of (±)-kelsoene

2.5.2 Total synthesis of (±)-kelsoene

The planned total synthesis of (±)-kelsoene required an efficient synthesis of the diquinane core structure ***rac*-34**. A review of the literature revealed that in spite of the large body of work related to cyclopentane annulation methods[60,61] and polyquinane natural product synthesis,[62] only a couple of methods exist which establish the desired relationship between the ketone and the alkene moieties present in ***rac*-34**.

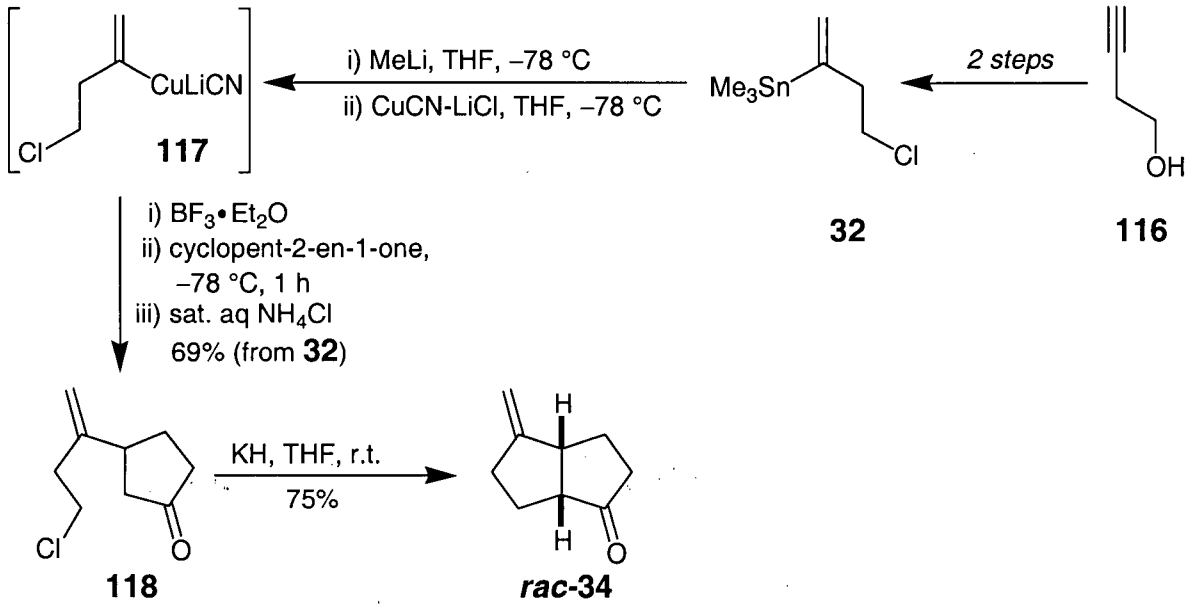
The preparation of alkenone ***rac*-34** reported by Franck-Neumann and Kastler.[63] (**Scheme 2.20**) relies on the trimethylamine oxide mediated decomplexation of a tricarbonyl [trimethylenemethane] iron complex bearing an enone (**115**). Unfortunately, this reaction and the synthesis of the necessary starting material both proceed in low yield.



114 115 ***rac*-34**

Scheme 2.20: Franck-Neumann's synthesis of alkenone *rac*-34[63]

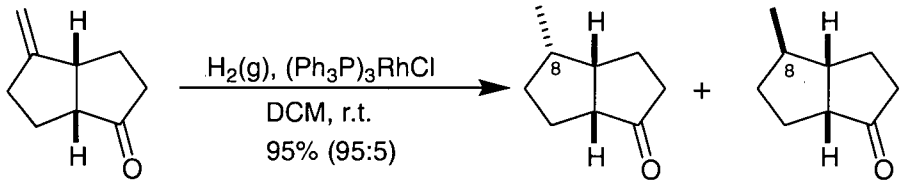
It was decided to synthesize ketone ***rac*-34** using a procedure modified from that reported earlier by this research group.[32] The bifunctional reagent 4-chloro-2-trimethylstannylbut-1-ene (**32**) was prepared from 3-butyn-1-ol (**116**) in two steps using the method devised by Piers and Chong[31] (**Scheme 2.21**). Sequential treatment of this material with MeLi and CuCN-LiCl in THF afforded the "lower order" heterocuprate[64] lithium cyano(4-chlorobut-1-en-2-yl)cuprate (**117**). Reaction of this reagent with commercially available cyclopent-2-en-1-one in the presence of $BF_3 \bullet Et_2O$, followed by a suitable workup procedure, provided the conjugate addition product **118** in good yield. Treatment of **118** with KH in THF caused an intramolecular alkylation reaction that provided the desired alkenone.



118 ***rac*-34**

Scheme 2.21: Synthesis of alkenone *rac*-34

With an efficient synthesis of alkenone ***rac*-34** accomplished, the stage was set to establish the correct configuration at C-8 (kelsoene numbering) through a stereoselective hydrogenation of the exocyclic alkene. It appeared likely that this hydrogenation would, for steric reasons, occur predominantly from the convex face of the bicycle. However, treatment of ***rac*-34** with hydrogen in the presence of palladium-on-carbon provided ketones ***rac*-59** and **119** (see **Scheme 2.22**) in nearly equal amounts. Fortunately, the use of homogeneous hydrogenation catalysts gave better results. Thus, hydrogenation of ***rac*-34** using Crabtree's catalyst ($[Ir(cod)py(Pcy_3)]PF_6$)[65] furnished ketones ***rac*-59** and **119** in a ratio of 6:1, but the hydrogenation proceeded at a very slow rate. On the other hand, reduction of ***rac*-34** with hydrogen in the presence of Wilkinson's catalyst[66] afforded a 95% yield of a mixture of ***rac*-59** and **119** in a ratio of 95:5 as determined by ^{1}H-NMR spectroscopy (**Scheme 2.22**). At this stage no experiments were carried out to verify the relative configuration of the major product. These diastereomers proved difficult to separate and, therefore, were carried through the next synthetic operation as a mixture.



***rac*-34** ***rac*-59** **119**

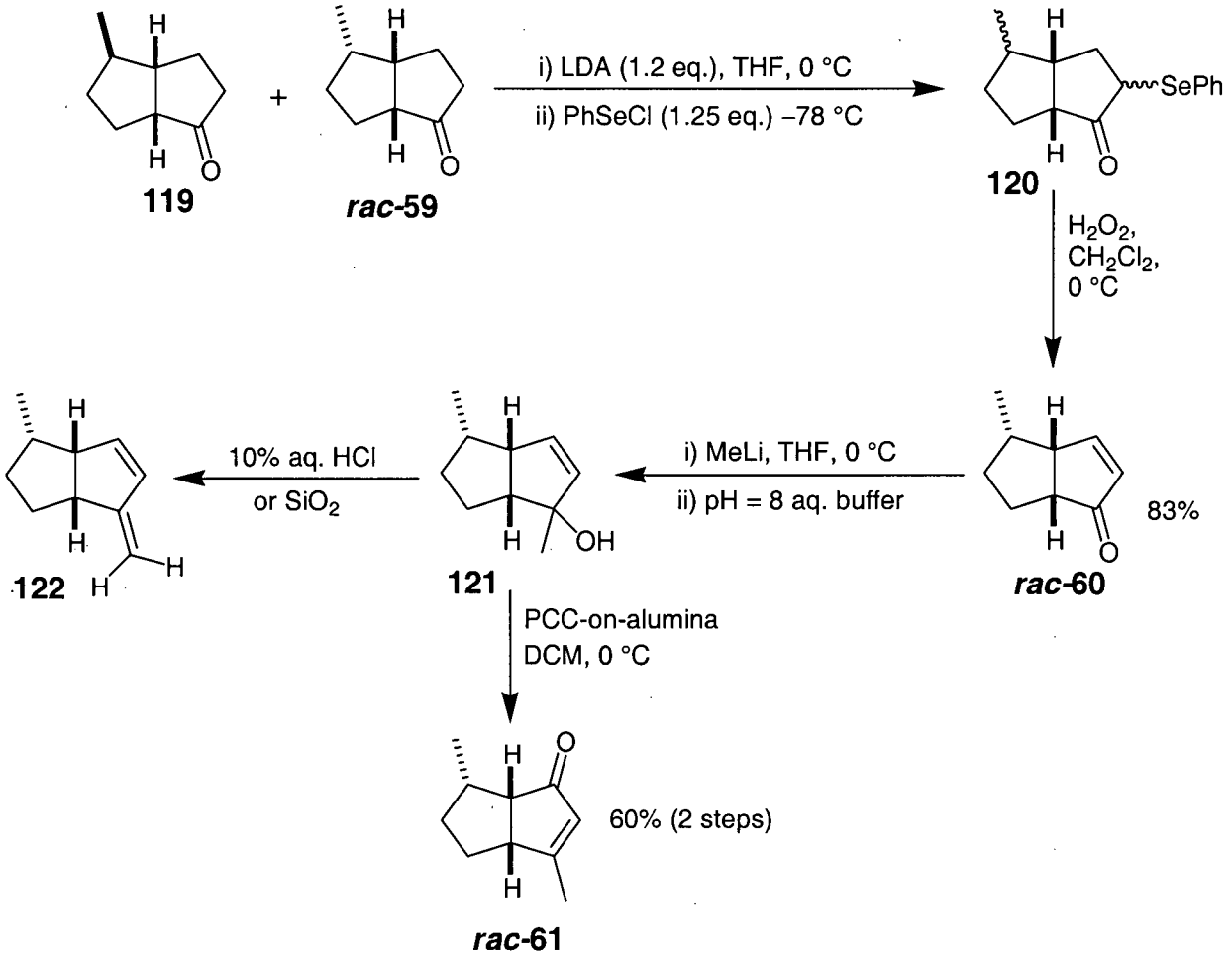
Scheme 2.22: Diastereoselective hydrogenation of alkenone *rac*-34

The spectral data collected on ketone ***rac*-59** was in full accord with the structural assignment of the compound. The IR spectrum of ***rac*-59** displayed a strong C=O stretching absorption (1736 cm^{-1}) characteristic of a saturated five-membered ring ketone. In addition, the ^{13}C NMR spectrum recorded for ***rac*-59** included a carbonyl resonance at δ = 223.1. Furthermore, the ^{1}H NMR spectrum displayed a 3-proton doublet at δ = 0.97, with a coupling constant of 6.9 Hz, which could be attributed to the methyl group at C-8 (kelsoene numbering). Finally, an HRMS measurement on the parent ion revealed that the material obtained from the hydrogenation had a molecular formula consistent with the structure of ketone ***rac*-59**.

Ketone ***rac*-59** was converted into the desired photocycloaddition precursor using a three-step sequence (**Scheme 2.23**). Oxidation of the 95:5 mixture of ketones ***rac*-59** and **119** to the corresponding enones was accomplished using the method established by Reich *et al.*[67,68] Thus the mixture of ketones was treated with an excess of LDA in order to form the corresponding kinetic enolates. These enolates were quenched with phenylselenenyl chloride to generate the requisite α-phenylselenides (**120**). Oxidation of the phenylselenides with hydrogen peroxide and chromatographic purification of the acquired material provided enone ***rac*-60** in 83% yield. No attempt to identify or isolate the enone derived from the minor ketone (**119**) was made.

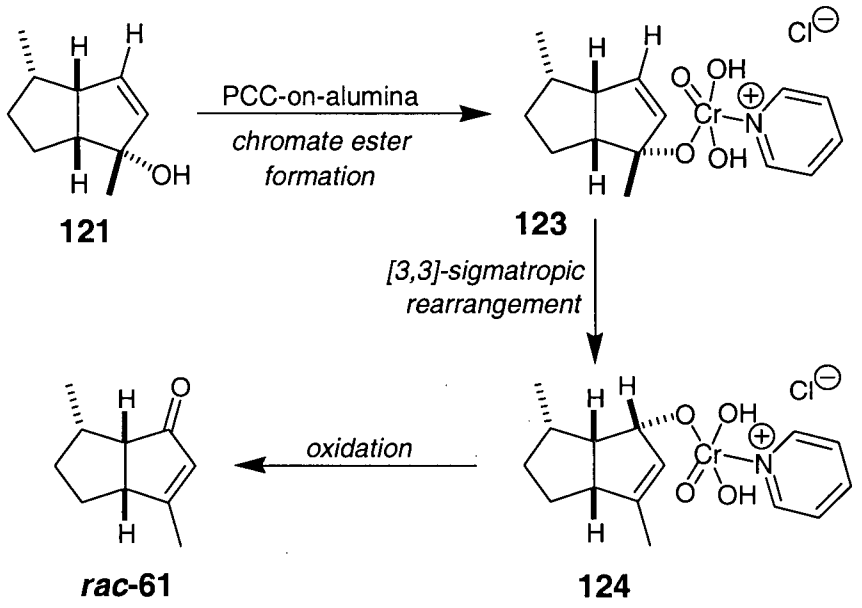
The spectroscopic data collected for enone ***rac*-60** was in full accord with the assigned structure. The IR spectrum of ***rac*-60** displayed a strong C=O stretching absorption at 1707 cm^{-1} that can be attributed to a conjugated carbonyl group. The ^{13}C NMR revealed an enone carbonyl resonance at δ = 213.7 and two olefinic carbon resonances at δ = 135.8 (α) and 165.3 (β). In addition, the ^{1}H NMR spectrum included two 1-proton resonances at δ = 6.17 (α) and 7.57 (β) with a mutual coupling constant of 5.8 Hz.

Enone ***rac*-60** was treated with an excess of methyllithium in THF at 0 °C to generate the expected tertiary allylic alcohol (**121**). This alcohol proved to be very prone to elimination. Treatment of the reaction mixture with 10% aq. HCl or exposure of the crude alcohol to silica gel resulted in the formation of conjugated diene **122**. Therefore, the isolation of the crude tertiary allylic alcohol required a work-up procedure which included a quench of the reaction mixture with a pH = 8 aqueous buffer.



Scheme 2.23: Synthesis of enone *rac*-61

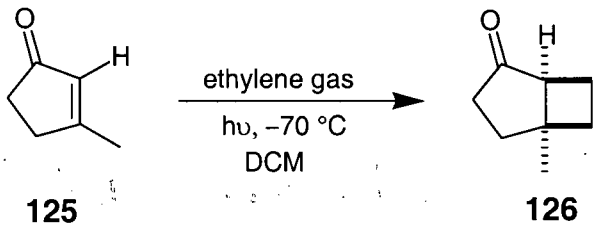
Finally, the crude tertiary allylic alcohol was treated with PCC-on-alumina[69-72] to generate the required conjugated enone (***rac*-61**, **Scheme 2.23**). This transformation occurs through the initial formation of a chromate ester (**123**) followed by a [3,3]-sigmatropic rearrangement and subsequent oxidation of the rearranged chromate ester (**124**, **Scheme 2.24**). This PCC-induced oxidative rearrangement of tertiary allylic alcohols has played a key role in the development of new cyclopentenone,[73] cyclohexenone[74] and cycloheptenone[34] annulation methods in this laboratory.



Scheme 2.24: PCC induced oxidative rearrangement of tertiary allylic alcohol 121

Analysis of the spectral data collected on enone ***rac*-61** verified the assigned structure. The IR spectrum of this material included the diagnostic absorption at 1698 cm^{-1} attributed to a conjugated carbonyl group. The ^{13}C NMR spectrum contained a carbonyl resonance at $\delta = 210.2$ and two olefinic resonances at $\delta = 132.4$ (α) and 179.6 (β). More importantly, the ^{1}H NMR spectrum included a 3-proton singlet at $\delta = 2.02$ attributed to the alkenyl methyl group. In addition, a single 1-proton broad singlet ($\delta =$ 5.82-5.84) was observed in the olefinic region of the spectrum.

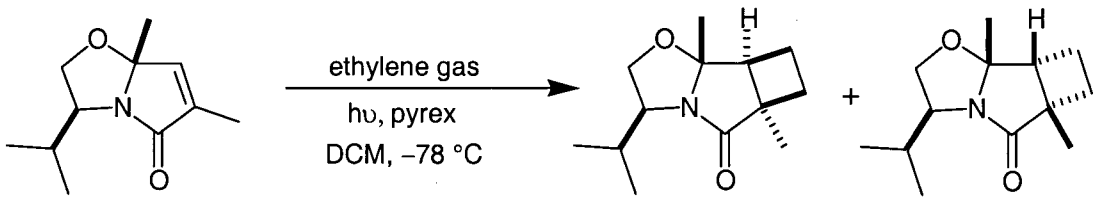
The plan for the synthesis of (±)-kelsoene called for a [2+2]-photocycloaddition reaction to construct the four membered ring. This strategy was based on two literature reports in which the efficient synthesis of four membered rings through similar [2+2]-photocycloadditions had been demonstrated. Caldwell and coworkers[58] showed that when a solution of enone **125** in DCM saturated with ethylene gas at −70 °C is irradiated with UV-light through a Pyrex filter, bicyclic ketone **126** is obtained in 90% yield (**Scheme 2.25**).



125 126

Scheme 2.25: [2+2]-photocycloaddition of ethylene to 3-methylcyclopent-2-en-1-one (125)[58]

Similarly, Meyers[59] has demonstrated the synthesis of the tricyclic lactam **128** using similar conditions. In this case two tricyclic products, **128** and **129**, are observed in a 12:1 ratio, respectively (**Scheme 2.26**). Presumably, the approach of ethylene from the sterically less encumbered convex side of the α,β-unsaturated bicyclic lactam (**127**) provides the major product. In this case, the diastereocontrol imposed by the convex nature of the bicycle is less than would be expected with an enone such as ***rac*-61**, due to the presence of the angular methyl group which, to some extent, serves to block the approach of ethylene from the convex face. In addition, the sp^2 character of the nitrogen atom at the ring fusion reduces the effect of the convex nature of the bicyclic system.

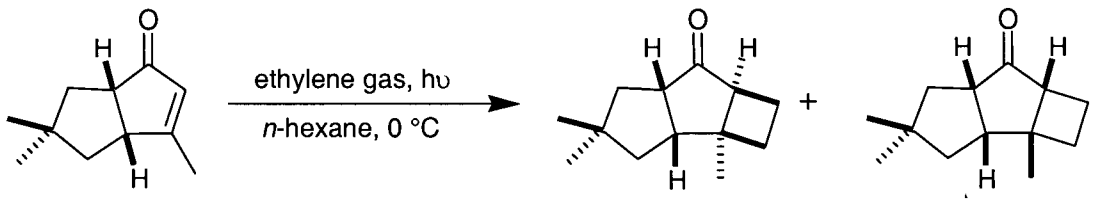


127 128 129

Scheme 2.26: [2+2]-photocycloaddition of ethylene to α,β-unsaturated bicyclic lactam 127[59]

At the time that the retrosynthetic analysis of kelsoene was carried out, a relevant report regarding [2+2]-photocycloadditions was overlooked. As it turns out, the synthesis of a tricyclic system very similar to that required for the synthesis of (±)-kelsoene has been carried out by Ohfune *et al.*[75] (**Scheme 2.27**). Thus, irradiation of

bicyclic enone **130** in the presence of ethylene provided a mixture of the *cis-anti-cis*-photoproduct **131** and its *cis-syn-cis* isomer **132** in 75% and 8% respectively. That the *cis-syn-cis*-photoproduct was obtained in a significant amount indicates that the convex nature of the bicyclic enone is not sufficient to provide complete selectivity in the photocycloaddition.

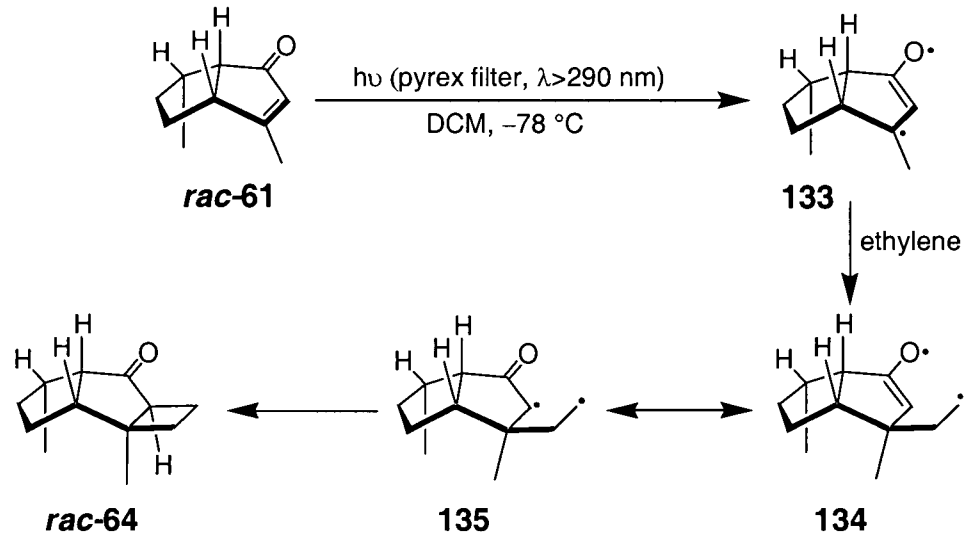


130 **131** **132**

Scheme 2.27: [2+2]-photocycloaddition of ethylene to bicyclic enone 130[75]

With a sufficient amount of enone ***rac*-61** and significant literature precedent for the desired photocycloaddition, the stage was set to attempt the construction of the requisite tricyclic ketone (***rac*-64**). Irradiation of a DCM solution of enone ***rac*-61** saturated with ethylene gas at −78 °C with UV-light through a Pyrex filter provided the expected *cis-anti-cis* tricyclic ketone in 90% yield (**Scheme 2.28**). The absence of the isomeric *cis-syn-cis* tricycle, and the high yield of the reaction indicates that the secondary methyl substituent in enone ***rac*-61** exerts some diastereocontrol beyond that provided by the convex nature of the bicyclic system.

This reaction is thought to proceed through a stepwise mechanism (**Scheme 2.28**).[76,189] The first step involves an $n \rightarrow \pi^*$ transition of enone ***rac*-61** to its triplet excited state (**133**), which behaves as a biradical and reacts with ethylene to generate a biradical adduct. This species can be represented as resonance forms **134** and **135**. A radical recombination closes the four membered ring to furnish the desired *cis-anti-cis* tricycle.



rac-61 133 *rac*-64 135 134

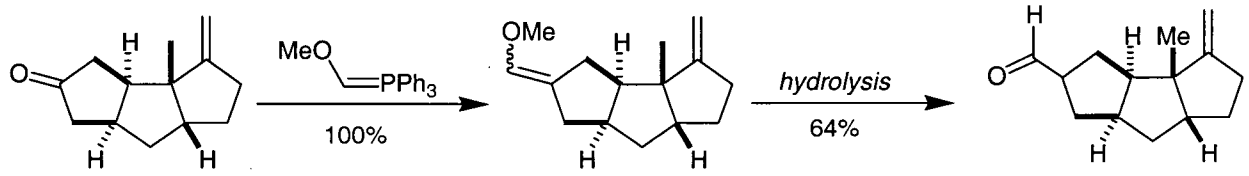
Scheme 2.28: synthesis of tricyclic ketone *rac*-64

The spectral data collected on ketone ***rac*-64** supported the assigned structure. The IR spectrum showed a strong absorption at 1728 cm^{-1}, which is diagnostic of a saturated 5-membered ring ketone. The ^{13}C NMR spectrum contained the correct number of carbon resonances, including a carbonyl resonance at $\delta = 223.4$. The olefinic carbon resonances previously observed in enone ***rac*-61** were absent. Analysis of a separate APT experiment revealed the presence of 2 methyl, 4 methylene and 4 methine carbon resonances. Moreover, an HRMS measurement on the parent ion was consistent with the molecular formula corresponding to ketone ***rac*-64**.

Thus, the tricyclic core of (±)-kelsoene, with the correct relative configuration at each of the five carbon chirality centers, had been assembled from commercially available cyclopent-2-en-1-one and the known bifunctional reagent 4-chloro-2-trimethylstannylbut-1-ene (**32**) in eight synthetic operations. All that remained to complete the synthesis of kelsoene was the installation of the isopropenyl group with the correct relative configuration at C-6 (kelsoene numbering).

As originally planned, the total synthesis of (±)-kelsoene would proceed with the homologation of tricyclic ketone ***rac*-64** to the corresponding aldehyde. This transformation was expected to occur through a Wittig olefination of ketone ***rac*-64** with

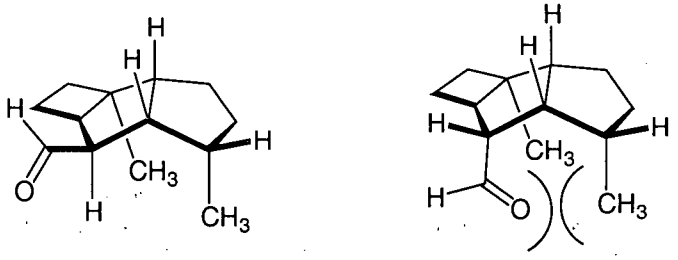
(methoxymethylene)triphenylphosphorane to generate the corresponding exocyclic methyl enol ether. This substance would, in turn, be hydrolyzed under acidic conditions to furnish the homologated aldehyde. This sequence has been successfully employed in triquinane sesquiterpenoid synthesis (**Scheme 2.29**).[77]



136 **137** **138**

Scheme 2.29: Homologation of ketone 136 to aldehyde 138 in a study towards the synthesis of hirsutene[77]

In the present work, the configuration of the aldehyde was expected to be that required for the synthesis of kelsoene due to a significant non-bonded interaction between the C-8 methyl group and the α-oriented aldehyde (***rac*-80**). This interaction is absent in the required β-oriented aldehyde (**139**, **Figure 2.4**)

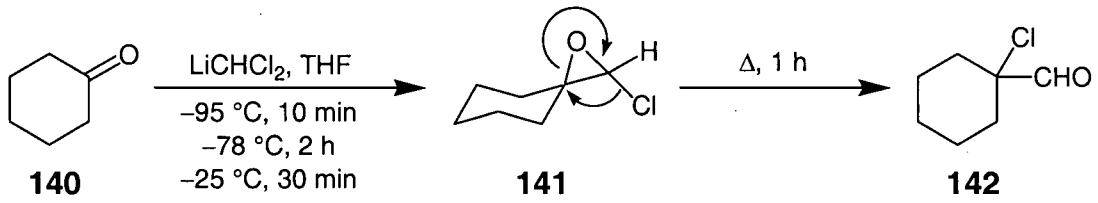


139 ***rac*-80**

Figure 2.4: Steric interactions between the C-8 methyl group and the C-6 aldehyde in 139 and *rac*-80

Surprisingly, subjection of ketone ***rac*-64** to the homologation conditions previously described (*vide supra*) did not provide the desired methyl enol ether, and resulted only in recovery of the starting material. Initially, it was thought that the bulky nature of the phosphorane reagent was the major cause for the lack of reaction.

Therefore, alternative methods involving sterically less hindered reagents were sought. In this connection, Taguchi *et al.*[78] have shown that ketones can be homologated to the corresponding α-chloroaldehydes under the action of dichloromethyllithium at low temperatures, followed by heating of the initial adduct (**Scheme 2.30**). It is believed that the initial 1,2-addition product undergoes a ring closing reaction to the chloro epoxide (**141**), releasing a chloride ion as a leaving group. Heating of chloroepoxide **141** promotes its rearrangement to α-chloroaldehyde **142**.

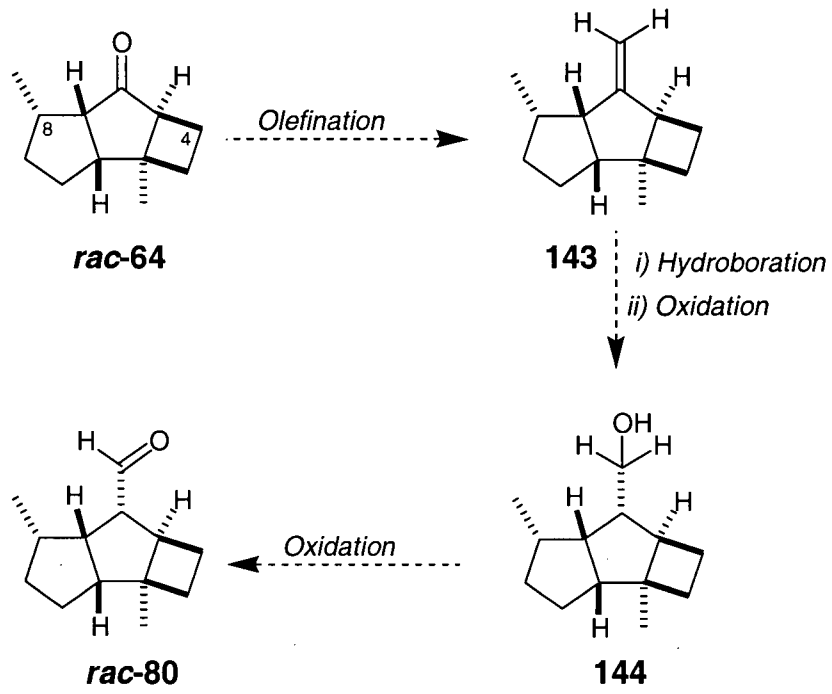


140 **141** **142**

Scheme 2.30: Taguchi's synthesis of an α-chloroaldehyde from cyclohexanone[78]

Unfortunately, the attempted application of this method in the synthesis of (±)-kelsoene was unsuccessful, as the reaction of dichloromethyllithium with ketone ***rac*-64** provided an intractable mixture of products.

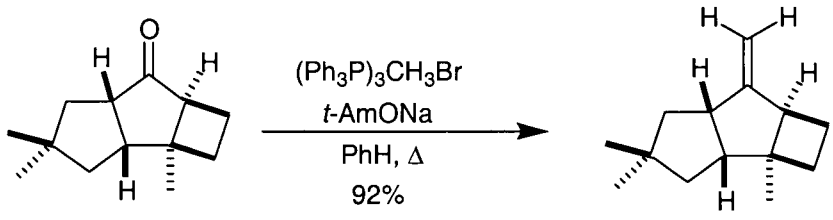
It became apparent that, in order to accomplish the desired homologation, the original synthetic plan required some strategic modification. The revised approach relied on the formation of an exocyclic olefin (**143**) from ketone ***rac*-64**, likely through the use of a relatively small organometallic reagent. This exocyclic olefin could then be hydroborated and oxidized to provide a primary alcohol (**144**), and elaborated to the target aldehyde (**Scheme 2.31**).



***rac*-64** **143** **144** ***rac*-80**

Scheme 2.31: Modified synthetic plan to aldehyde *rac*-80

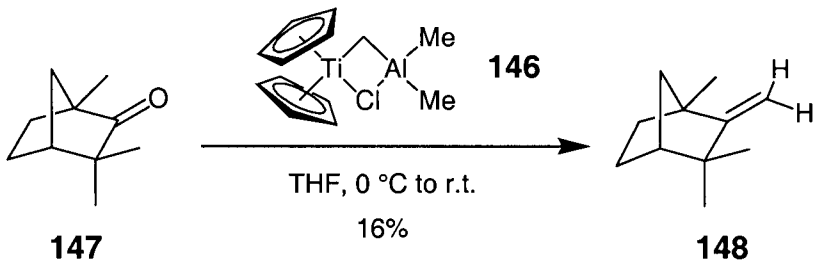
It was expected that the olefination of ketone ***rac*-64** could be carried out through the use of a Wittig protocol. Indeed, precedent for this transformation on a very similar substrate (**131**) exists in the literature (**Scheme 2.32**).[75] It was, therefore, somewhat surprising that reaction of ketone ***rac*-64** with methylenetriphenylphosphorane resulted only in the recovery of starting material. This result, and the successful olefination of ketone ***rac*-65** carried out by Mehta and Srinivas (**Scheme 2.7**) suggest that the lack of reactivity observed with ketone ***rac*-64** is largely due to the steric congestion imposed by presence of the C-8 methyl group and the C-4 methylene group (kelsoene numbering, *vide supra*).



131 **145**

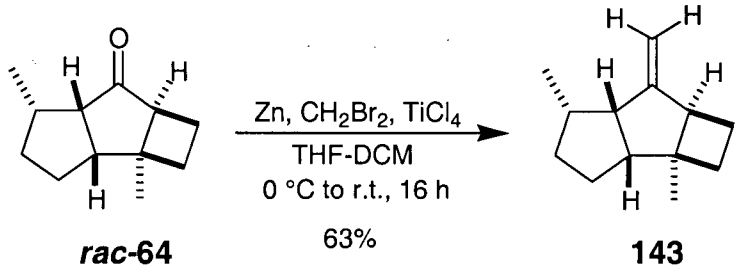
Scheme 2.32: Wittig olefination of ketone 131[75]

The difficulties associated with methylenation of sterically hindered ketones have been well documented. Titanium based methylenating reagents have surfaced as superior alternatives to the Wittig phosphoranes.[79] A comparative study[80] revealed that the Tebbe reagent (**146**)[81] is comparable to or more effective than the Wittig reagent in most cases. However, highly hindered ketones such as fenchone (**147**) still fail to give satisfactory results (**Scheme 2.33**). Thus, it was not surprising that the attempted methylenation of tricyclic ketone ***rac*-64** with Tebbe's reagent did not provide the desired olefin.



Scheme 2.33: Olefination of fenchone with Tebbe's reagent[80]

Takai *et al.* developed a similar titanium based reagent which is more reactive than the Tebbe reagent and which is still not well characterized.[82-84] An alternative method for the preparation of the active species has been developed by Lombardo,[85,86] and both methods have proven successful in the methylenation of hindered and easily enolizable ketones. Gratifyingly, subjection of ketone ***rac*-64** to the olefination conditions described by Lombardo provided the desired alkene in 63% yield after a reaction time of 16 hours[87] (**Scheme 2.34**).



***rac*-64** **143**

Scheme 2.34: Lombardo olefination of ketone *rac*-64

The spectral data collected on olefin **143** was in full support of the assigned structure. The ^{13}C NMR spectrum showed the correct number of carbon resonances, including two alkene resonances at δ = 108.8 (exocyclic) and 159.9 (endocyclic). Analysis of a separate APT experiment revealed 2 methyl, 5 methylene and 4 methine resonances. Moreover, the newly introduced exocyclic methylene group was observed as a 2-proton multiplet at δ = 4.90-4.95 of the ^{1}H NMR spectrum.

Having synthesized the requisite exocyclic olefin, the stage was set to attempt the hydroboration of this material. Based on the lack of reactivity observed with ketone ***rac*-64**, it seemed likely that bulky hydroboration reagents such as 9-BBN would fail at achieving the desired transformation. Therefore, the hydroboration of compound **143** was attempted using borane-dimethyl sulfide complex. It was expected that the hydroboration would proceed with a high degree of regioselectivity and facial selectivity. With respect to facial selectivity, analysis of molecular models indicates that the hydroborating reagent should approach the alkene moiety from the less sterically hindered β-face to furnish alcohol **144**, which possesses the incorrect relative configuration at the newly formed carbon chirality center (**Figure 2.5**).

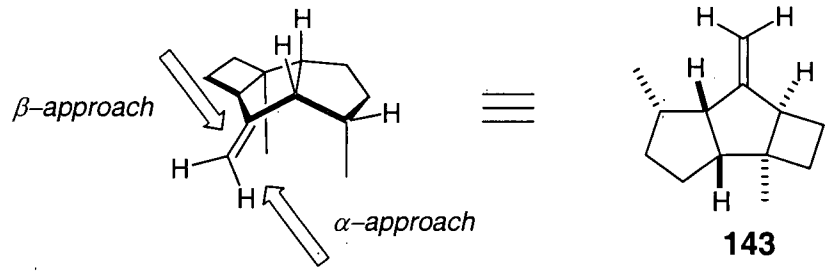
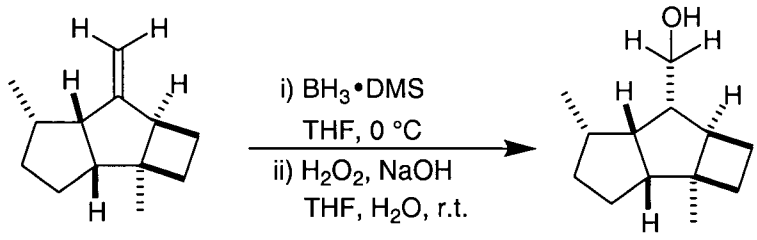


Figure 2.5: Approach of a hydroborating reagent to olefin 143

The hydroboration of alkene **143** proceeded with a high degree of regio- and facial-selectivity and in good yield (**Scheme 2.35**). At this stage it was deemed prudent to verify the structure of this substance, and to ascertain the relative configuration of its six carbon chirality centers. To this end, the IR, HRMS, ^{1}H NMR, ^{13}C NMR, HMQC, HMBC and COSY spectra of this substance were recorded. As expected, the IR spectrum of this material contained an absorption at 3325 cm^{-1} due to the primary

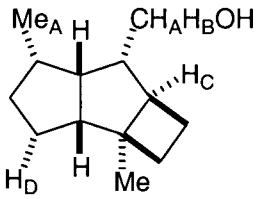
alcohol moiety. The ^{13}C NMR spectrum exhibited a resonance at $\delta = 64.7$ attributed to the carbinol carbon. The ^{1}H NMR spectrum showed two doublets-of-doublets at $\delta =$ 3.33 and 3.93, with a mutual coupling constant of 10.2 Hz, which can be attributed to the carbinol protons. Finally, an HRMS measurement on the parent ion was consistent with the molecular formula of the expected alcohol.



143 **144**

Scheme 2.35: Synthesis of alcohol 144

Due to a fortuitous dispersion of signals, the ^{1}H NMR spectrum of alcohol **144** could be fully assigned (see experimental section for details). A set of one dimensional NOE difference experiments verified that the configuration at the newly generated carbon chirality center was as expected (*vide supra*). As shown below, the secondary methyl group (Me_A) in alcohol **144** gives rise to a doublet at δ = 1.02, the carbinol protons H_A and H_B produce doublets of doublets at δ = 3.33 and δ = 3.93, and the signals due to the tertiary and secondary hydrogens H_C and H_D appear as multiplets at δ = 2.30 and δ = 1.34 respectively (**Figure 2.6**).



144

Me_A: δ = 1.02 (d); signal enhanced by irradiation at δ = 3.33 or 3.93

H_A, H_B: δ = 3.33 (dd), 3.93 (dd)

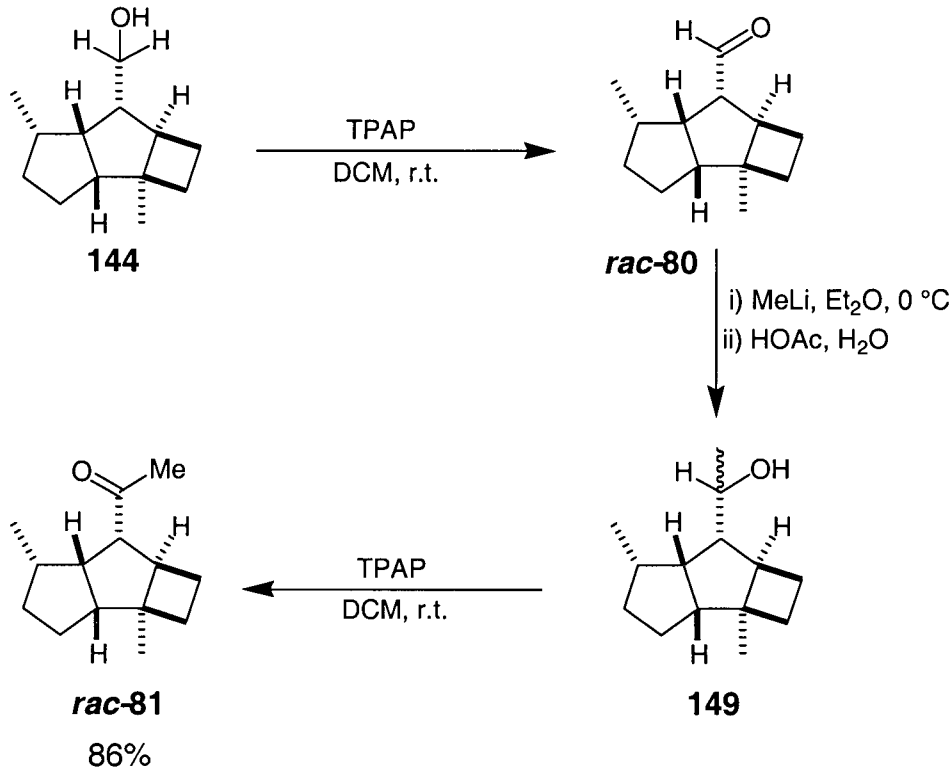
H_C: δ = 2.30 (m); signal enhanced by irradiation at δ = 3.33 or 3.93

H_D: δ = 1.34 (m); signal enhanced by irradiation at δ = 3.33

Figure 2.6: NOE correlations in alcohol 144

In nuclear Overhauser enhancement difference (NOED) experiments, irradiation at either δ = 3.33 or δ = 3.93 (H_A, H_B) enhances the signal intensities at both δ = 1.02 (Me_A) and δ = 2.30 (H_C). Also, irradiation at δ = 3.33 (H_A or H_B) causes an increase in the intensity of the resonance at δ = 1.34 (H_D). These experiments show clearly that the CH_2OH function is on the α-face of the molecule as drawn above (**144**, **figure 2.6**).

The next step in the sequence involved the oxidation of alcohol **144** to the corresponding aldehyde. This was accomplished smoothly and in high yield using the method developed by Ley *et al.*[88] (**Scheme 2.36**). The aldehyde obtained (***rac*-80**) proved quite unstable and was therefore used shortly after its preparation. However, the IR spectrum of ***rac*-80** showed an absorption at 1716 cm^{-1}, indicative of the aldehyde moiety. Furthermore, an HRMS measurement of the parent ion was consistent with the molecular formula of the expected aldehyde. Addition of methyllithium to aldehyde ***rac*-80**, and oxidation[88] of the resultant diastereomeric mixture of secondary alcohols provided ketone ***rac*-81** in 86% yield from alcohol **144**.

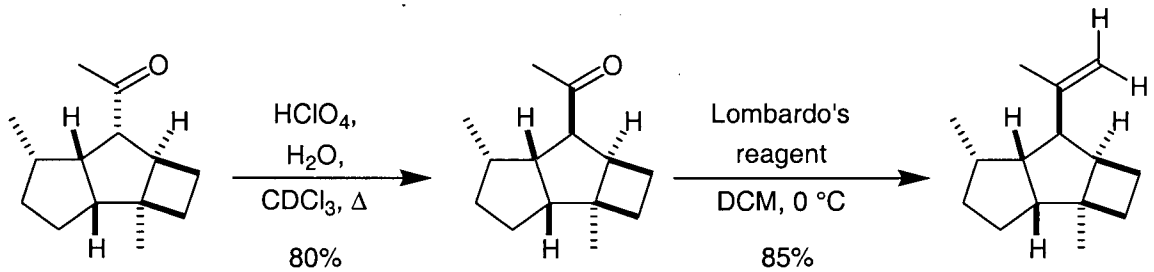


Scheme 2.36: Synthesis of ketone *rac*-81

The structure of ketone ***rac*-81** was verified with the usual spectroscopic techniques. Thus, the IR spectrum showed the expected absorption for the ketone carbonyl stretch at 1707 cm^{-1}. The ^{13}C NMR spectrum contained the expected number of carbon resonances, including a carbonyl resonance at δ = 210.0. Finally, the ^{1}H NMR spectrum included a three-proton singlet at δ = 2.19 attributed to the newly introduced methyl group.

At this stage it was necessary to invert the configuration of the chirality center associated with the acetyl group. This operation was accomplished by refluxing a biphasic mixture consisting of a deuteriochloroform solution of ketone ***rac*-81** and a solution of perchloric acid in water (**Scheme 2.37**). The required epimeric ketone ***rac*-70** was obtained in 80% yield and showed a carbonyl stretch absorption at 1709 cm^{-1} in the IR spectrum. The expected carbonyl resonance appeared at δ = 208.7 in the ^{13}C NMR spectrum. Furthermore, the methyl group associated with the acetyl moiety appeared as a three-proton singlet at δ = 2.02.

All that remained to complete the synthesis of kelsoene was the transformation of the ketone moiety in ***rac*-70** into the corresponding olefin. This was accomplished in high yield through the use of Lombardo's reagent (**Scheme 2.37**). The ^{13}C NMR, ^{1}H NMR, IR and HRMS spectral data collected on the synthetic sample of (±)-kelsoene are in full accordance with that reported for (+)-kelsoene by Konig and Wright[37] (see **Tables 2.1**, **2.2**, and **2.3**).



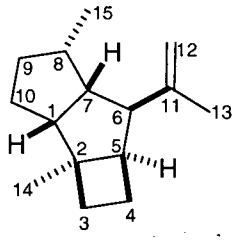
***rac*-81** ***rac*-70** **(±)-kelsoene**

Scheme 2.37: Completion of the synthesis of (±)-kelsoene

Table 2.1. Comparison of the HREIMS and IR data reported for naturally occurring (+)-kelsoene with the HRMS and IR data obtained for synthetic (±)-kelsoene

Data	naturally occurring (+)-kelsoene	synthetic (±)-kelsoene
IR (cm^{-1})	3085	3083
	1650	1647
	1450	1452
	1375	1374
	885	886
HREIMS (*m/z*)	204.1869	204.1870

Table 2.2. Comparison of the ^{13}C NMR data reported for naturally occurring (+)-kelsoene with the ^{13}C NMR data obtained for synthetic (±)-kelsoene

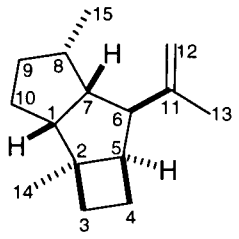


carbon number	δ (ppm)	
	naturally occurring (+)-kelsoene[a,b]	synthetic (±)-kelsoene[c]
1	57.8	57.8
2	45.7	45.8
3	33.0	33.1
4	14.6	14.6
5	47.4	47.5
6	48.1	48.1
7	49.9	50.0
8	36.3	36.3
9	33.2	33.3
10	26.0	26.0
11	145.6	145.6
12	109.8	109.8
13	24.1	24.1
14	23.5	23.5
15	17.7	17.7

[a] Assignments are as reported by Konig and Wright.[37]

[b] Recorded at 75 MHz in $CDCl_3$. [c] Recorded at 100 MHz in $CDCl_3$.

Table 2.3. Comparison of the ^{1}H NMR data reported for naturally occurring (+)-kelsoene and the ^{1}H NMR data obtained for synthetic (±)-kelsoene



proton number[a,b]	δ (ppm)(mult; *J* (Hz))	
	naturally occurring (+)-kelsoene[c]	synthetic (±)-kelsoene[d]
H-1	2.09 (ddd, 9.1, 8.9, 6.7)	2.06 (ddd, 9, 9, 6.8)
H-3a	1.64 (m)	part of the m at 1.61-1.69
H-3b (or H-4b	1.68 (m)	see footnote e
H-4a	1.52 (m)	part of the m at 1.43-1.54
H-4b (or H-3b)	1.68 (m)	see footnote e
H-5	2.42 (m)	part of the m at 2.31-2.41
H-6	2.37 (m)	part of the m at 2.31-2.41
H-7	2.87 (ddd, 10.5, 6.8, 6.7)	2.84 (ddd, 10.4, 7, 7)
H-8	2.27 (m)	2.24 (m)
H-9a	1.34 (m)	part of the m at 1.24-1.40
H-9b	1.76 (m)	part of the m at 1.69-1.81
H-10a	1.35 (m)	part of the m at 1.24-1.40
H-10b	1.47 (m)	part of the m at 1.43-1.54
H-12a	4.80 (br s)	4.77 (s)
H-12b	4.87 (br s)	4.84 (s)
H-13	1.61 (br s)	1.59 (s)
H-14	1.17 (s)	1.14 (s)
H-15	0.91 (d, 6.8)	0.89 (d, 7.0)

[a] Assignments are as reported by Konig and Wright.[37]

[b] Methylene protons are designated H-Xa and H-Xb arbitrarily.

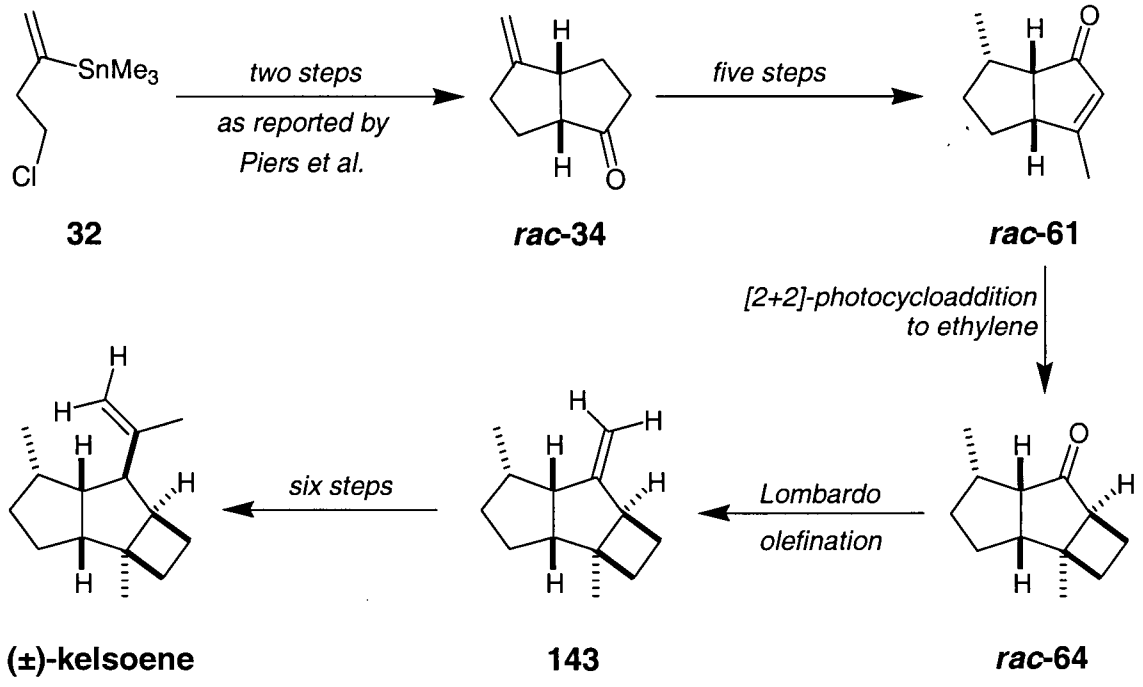
[c] Recorded at 300 MHz in $CDCl_3$.

[d] Recorded at 500 MHz in $CDCl_3$.

[e] H-3b and H-4b account for a proton at δ = 1.61-1.69 and a proton at δ = 1.69-1.81, but could not be unambiguously assigned.

2.5.3 Summary

The total synthesis of the unique natural product (±)-kelsoene (***rac*-35**) was accomplished[89] through a 15-step sequence from commercially available cyclopent-2-en-1-one and the bifunctional reagent 4-chloro-2-trimethylstannylbut-1ene[31] (**32, Scheme 2.38**). The synthetic approach was guided by the realization that the diquinane core of the natural product (***rac*-34**) could be assembled quickly and efficiently through an annulation method previously reported by this group.[32] Enone ***rac*-61** was prepared form ketone ***rac*-34** in a straightforward manner. A highly diastereoselective [2+2]-photocycloaddition of ethylene to enone ***rac*-61** served to install the cyclobutane ring of (±)-kelsoene. Tricyclic ketone ***rac*-64** could not be elaborated to the natural product using the original synthetic plan due to the severe steric congestion around its carbonyl group. This problem was circumvented through the use of Lombardo's reagent, which is reactive towards highly hindered and easily enolizable ketones, to generate the corresponding olefin (**143**). The natural product was obtained from olefin **143** through an efficient 6-step reaction sequence.

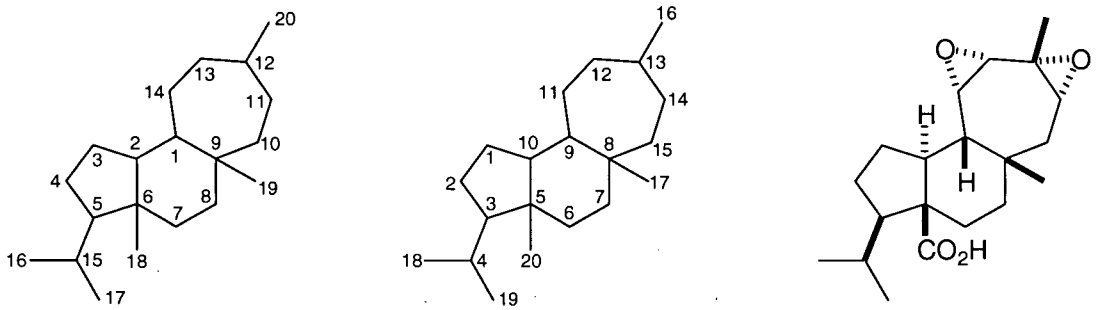


Scheme 2.38: Overview of the total synthesis of (±)-kelsoene

3. Synthetic Approaches to (±)-Isomulinic Acid

3.1 Introduction

The mulinane family of natural products comprises twelve diterpenoid substances, all of which possess the 5-isopropyl-6,9,12-trimethyltricyclo[7.5.0.$0^{2,6}$]-tetradecane framework depicted in structure **150** (**Figure 3.1**). Note that the carbon atoms of the parent tricycle are numbered according to the IUPAC nomenclature rules[90,91] for bridged hydrocarbons in **150**. The community of natural products chemists has adopted the numbering system depicted in **151** based on biosynthetic considerations.[33] For the sake of clarity, the numbering system depicted in **151** has also been adopted for sections **3.2** and **3.3** and **3.5** of this chapter.



150 **151** **(-)-isomulinic acid (39)**

Figure 3.1: Different numbering systems for the mulinane carbocyclic skeleton (150 and 151) and structure of (–)-isomulinic acid (39)

(–)-Isomulinic acid[33] (**39, Figure 3.1**) is arguably the most structurally complex member of the mulinane family of diterpenoids. Notable structural features embedded in this natural product include nine contiguous carbon chirality centers (two of which are quaternary), a tertiary carboxylic acid moiety, two epoxide rings, and a *trans*-fused hydrindane system. Clearly, this target compound presents a significant synthetic challenge.

3.2 Isolation, Structure Determination and Biological Activity

Mulinic acid (**152**) and isomulinic acid (**39, Figure 3.2**), the first reported members of the mulinane family of natural products, were isolated from the petrol extracts of *Mulinum crassifolium* Phil. (Umbelliferae) by Loyola *et al.*[33] This shrub is found in the north of Chile and its bitter infusions are used in folk medicine to treat diabetes and bronchial and intestinal disorders. The structure of mulinic acid (**152**) was elucidated using a combination of NMR spectroscopic and single-crystal X-ray diffraction analyses. The structure of isomulinic acid (**39**) was deduced using NMR spectroscopic analysis and by comparison of its spectral data with that obtained for mulinic acid (**152**). In addition, it was shown that isomulinic acid (**39**) can be obtained by heating a sample of mulinic acid (**152**) to 195 °C for 5 minutes. This thermal rearrangement proceeds with retention of configuration at C-11 and C-14.

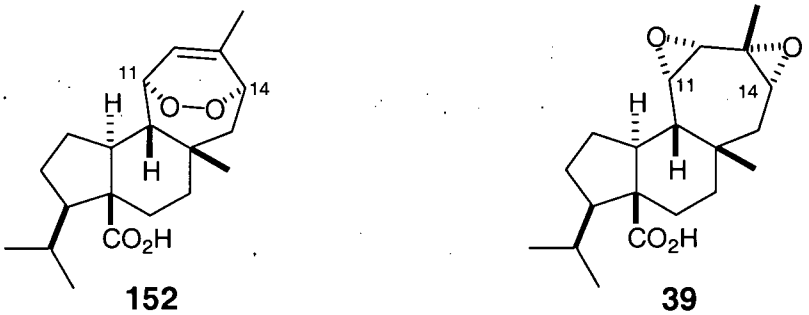
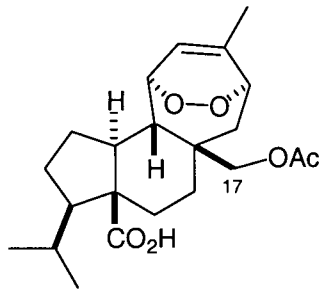


Figure 3.2: Structures of isomulinic acid (39) and mulinic acid (152)

Since the first report by Loyola *et al.*, ten other mulinane natural products have been isolated. 17-Acetoxymulinic acid (**153**),[92] mulinenic acid (**154**),[93] and mulinolic acid (**155**)[94] were also isolated from *Mulinum crassifolium* Phil. (Umbelliferae) (**Figure 3.3**). The structures of 17-acetoxymulinic acid and mulinolic acid were elucidated by analysis of their NMR spectral data. No determination of their absolute configuration was made, although it is postulated to be as depicted in **153** and **155** based on biogenetic considerations. The structure of mulinenic acid was determined to be as shown in structure **154** by analysis of NMR and X-ray crystallographic data.



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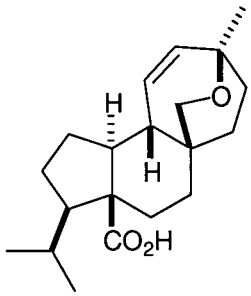
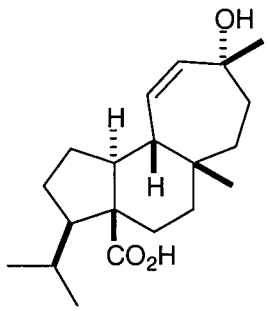


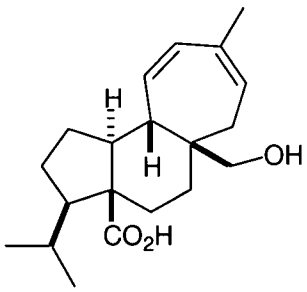
154



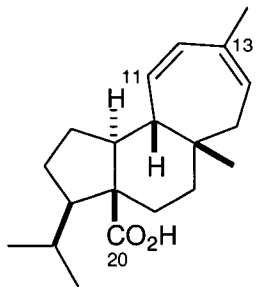
155

Figure 3.3: Structures of 17-acetoxymulinic acid (153), mulinenic acid (154) and mulinolic acid (155)

Nicoletti *et al.* disclosed the structures of two new mulinane diterpenoids from the extracts of *Mulinum spinosum* (Cav.) Pers.,[95] a shrub found in the Patagonia steppe of Chile and Argentina. Known as *neneo*, this plant is used in folk medicine to treat dental neuralgias, hepatic diseases and altitude sickness. The structures of compounds **156** and **157** were determined by analysis of their NMR spectral data (**Figure 3.4**).



156



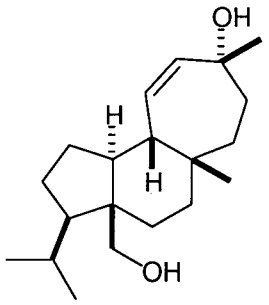
157

Figure 3.4: Structures of compounds 156 and 157

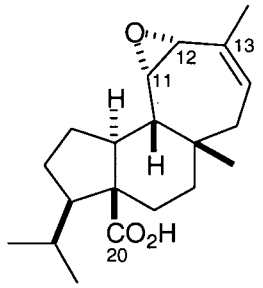
In 1997 Loyola *et al.* showed that compounds **155** (**Figure 3.3**) and **157** (**Figure 3.4**) also occur in *Azorella compacta* Phil. (Umbelliferae),[96] a resinous shrub which grows in the high Andes mountains of southern Peru, Bolivia, northwestern Argentina and northeastern Chile. Bitter tasting infusions of this plant are used in folk medicine for the treatment of diabetes, asthma, colds, bronchitis, and kidney and "womb

complaints." In this report, compound **157** is referred to as mulin-11,13-dien-20-oic acid.

Further investigation of the extracts of *Azorella compacta* Phil. (Umbelliferae) resulted in the isolation of two new mulinane natural products. The structures of mulinol (**158**) and 11,12-epoxymulin-13-en-20-oic acid (**159**)[97] were determined by analysis of their NMR spectral data (**Figure 3.5**).



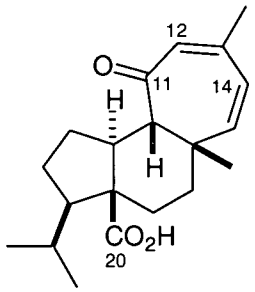
158



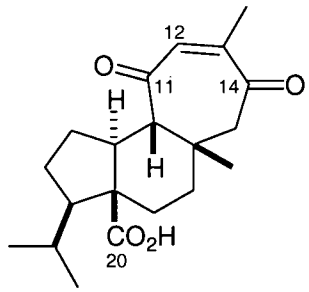
159

Figure 3.5: Structures of mulinol (158) and 11,12-epoxymuli-13-en-20-oic acid (159)

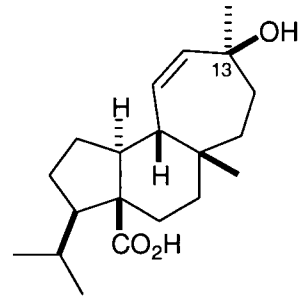
In 1999, Timmermann and coworkers[98] isolated two new mulinane diterpenoid natural products which, unlike all previously described mulinanes, displayed antibacterial activity. Mulin-12,14-dien-11-on-20-oic acid (**160**) and mulin-12-ene-11,14-dion-20-oic acid (**161**) were isolated from *Azorella compacta* Phil. (Apiaceae) (**Figure 3.6**). Finally, 13-epimulinolic acid (**162**) was isolated from the extracts of *Laretia acaulis* (Cav)[99] (**Figure 3.6**).



160



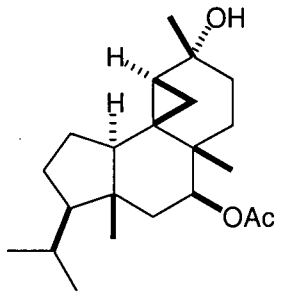
161



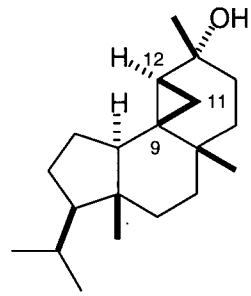
162

Figure 3.6: Structures of mulin-12,14-dien-11-on-20-oic acid (160), mulin-12-ene-11,14-dion-20-oic acid (161) and 13-epimulinolic acid (162)

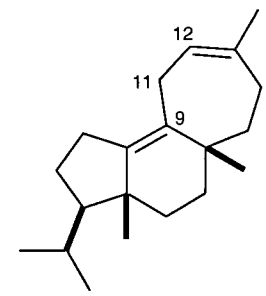
In 1998 Loyola *et al.* disclosed the structure of azorellanol (**163, Figure 3.7**), a diterpenoid substance with a new carbon skeleton isolated from *Azorella compacta* Phil. (Umbelliferae).[100] Recall that petrol extracts of this plant yielded a number of mulinane natural products. The same year Timmermann and coworkers disclosed the structure of a related natural product from *Azorella madreporica* Clos[101] (**164, Figure 3.7**). Compound **164** decomposes in $CDCl_3$ at room temperature. Interestingly, the major component in the mixture of decomposition products of compound **164** was shown to possess the mulinane carbocyclic skeleton (**165, Figure 3.7**).



azorellanol (163)



164



165

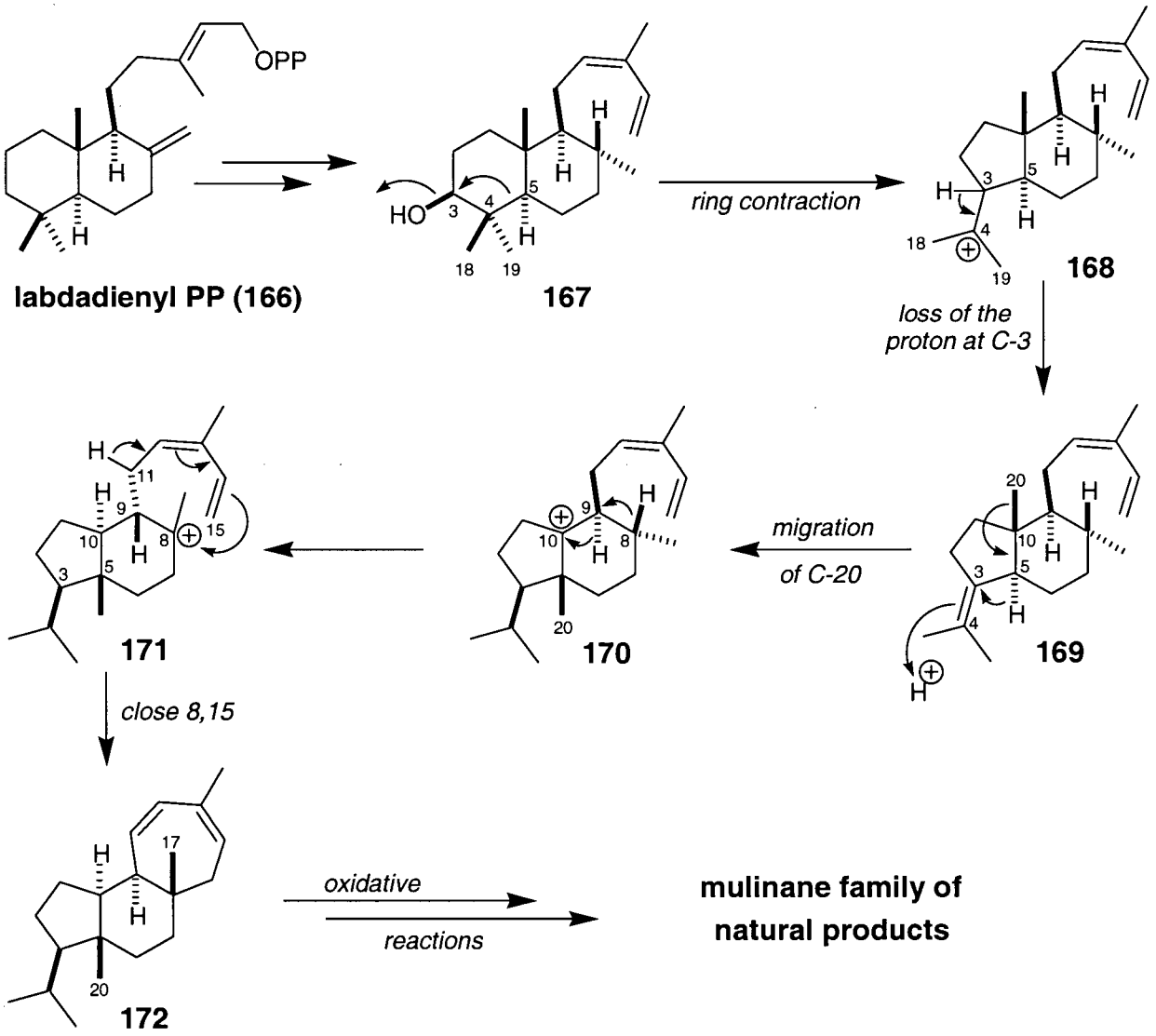
Figure 3.7: Structures of azorellanol (163) and compounds 164 and 165

3.3 Biogenesis

No biosynthetic studies have been carried out on the mulinane family of natural products. A possible biosynthetic pathway to the mulinane skeleton (**172**) from a labdane derivative (**167**) has been proposed by Loyola *et al.*[33] (**Scheme 3.1**).

The suggested biogenetic route to the mulinane family of natural products begins with alcohol **167**, which presumably is derived from labdadienyl pyrophosphate[102] (**166**) in a number of steps. The ring contraction that leads from alcohol **167** to compound **168** involves simultaneous cleavage of the bond between C-4 and C-5, bond formation between C-5 and C-3 and displacement of the hydroxyl group on C-3. This process leaves a positive charge localized at C-4 as shown in **168**. Loss of the proton from C-3 results in the formation of a double bond between C-3 and C-4 (see **169**). Migration of the methyl group from C-10 to C-5 occurs as shown in structure **169**. This sequence of steps establishes the relative configuration at C-3 and C-5, and leaves a positive charge localized at C-10 (see **170**). Two consecutive hydride shifts, as shown in **170**, establish the relative configuration at C-9 and C-10 and place the positive charge at C-8 (**170** to **171**). Carbon-carbon bond formation between C-8 and C-15, double bond migration and loss of a proton from C-11 as shown in **171** result in the formation of the mulinane tricyclic system (**172**). A number of oxidative reactions at C-17, C-20 and on the 7-membered ring of **172** give rise to the mulinane family of natural products.

It must be noted that Loyola *et al.* presented the biosynthetic pathway described above in their first report[33] of the mulinane diterpenoids. At that time, only two mulinanes (**39** and **152**) were known. In addition, the carbocyclic framework of the azorellane family of natural products (see **163** and **164** in **Figure 3.7** for example) was not reported until 1998. The structural similarity between the azorellane and mulinane families of natural products and their occurrence in the same organism suggests that they share a common biosynthetic pathway to an advanced intermediate (such as **171**) in which the relative configuration at C-3, C-5 and C-10 has been established.



Scheme 3.1: Proposed biosynthesis of the mulinane diterpenoids from a labdane precursor[33]

3.4 Synthetic Approaches to (±)-Isomulinic Acid

3.4.1 Introduction

The structural complexity of (–)-isomulinic acid (**39**) renders it a significant synthetic challenge, and this led us to attempt its total synthesis in racemic form. Our efforts in this regard evolved through four distinct strategies, each drawing upon the lessons learned from the previous failed attempt. The final strategy provided access to a tricyclic system reminiscent of the mulinane skeleton, with the correct relative configuration at the five carbon chirality centers present in all the members of the mulinane family of diterpenoids. Unfortunately, due to time and material constraints, completion of the total synthesis of (**39**) was not achieved despite our best efforts.

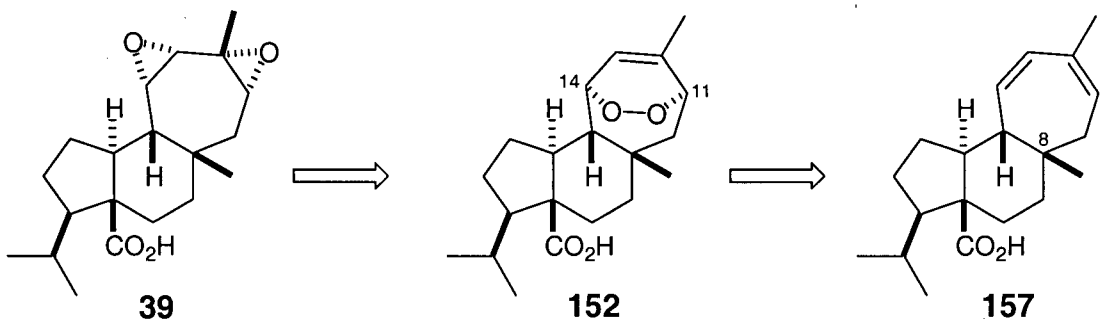
Although none of the synthetic plans presented in this chapter provided access to (±)-isomulinic acid, the retrosynthetic analysis leading to each of the four strategies is presented in order to provide context to the work that was carried out.

The reader should note that, for the sake of clarity, the numbering system adopted by the community of natural products chemists (see **151** in **Figure 3.1**) is used in the discussion dealing with the retrosynthetic analyses of isomulinic acid. All synthetic intermediates presented are numbered according to the IUPAC protocol for bridged carbocycles,[90,91] and any discussion related to them makes use of this system unless specified otherwise.

3.4.2 First approach to (±)-isomulinic acid

3.4.2.1 Retrosynthetic analysis

The retrosynthetic analysis of isomulinic acid (**39**) began with the realization that the two epoxides on its seven-membered ring can be obtained through the rearrangement of the endoperoxide moiety of mulinic acid (**152**, **Scheme 3.2**). Indeed, Loyola *et al.*[33] showed that this process occurs thermally. However, the yield for this transformation under these conditions was low. The same type of transformation is known to occur in high yield under the influence of transition metal catalysts.[103,104] Mulinic acid (**152**) can, in turn, be obtained through a hetero-Diels-Alder reaction of mulin-11,13-dien-20-oic acid (**157**) with singlet oxygen. Analysis of molecular models indicates that the methyl group on C-8 blocks the β-face of the diene on the seven-membered ring. Therefore, the hetero-Diels-Alder reaction of **157** with singlet oxygen should occur preferentially from the α-face of the molecule thereby establishing the correct relative configuration at C-11 and C-14.

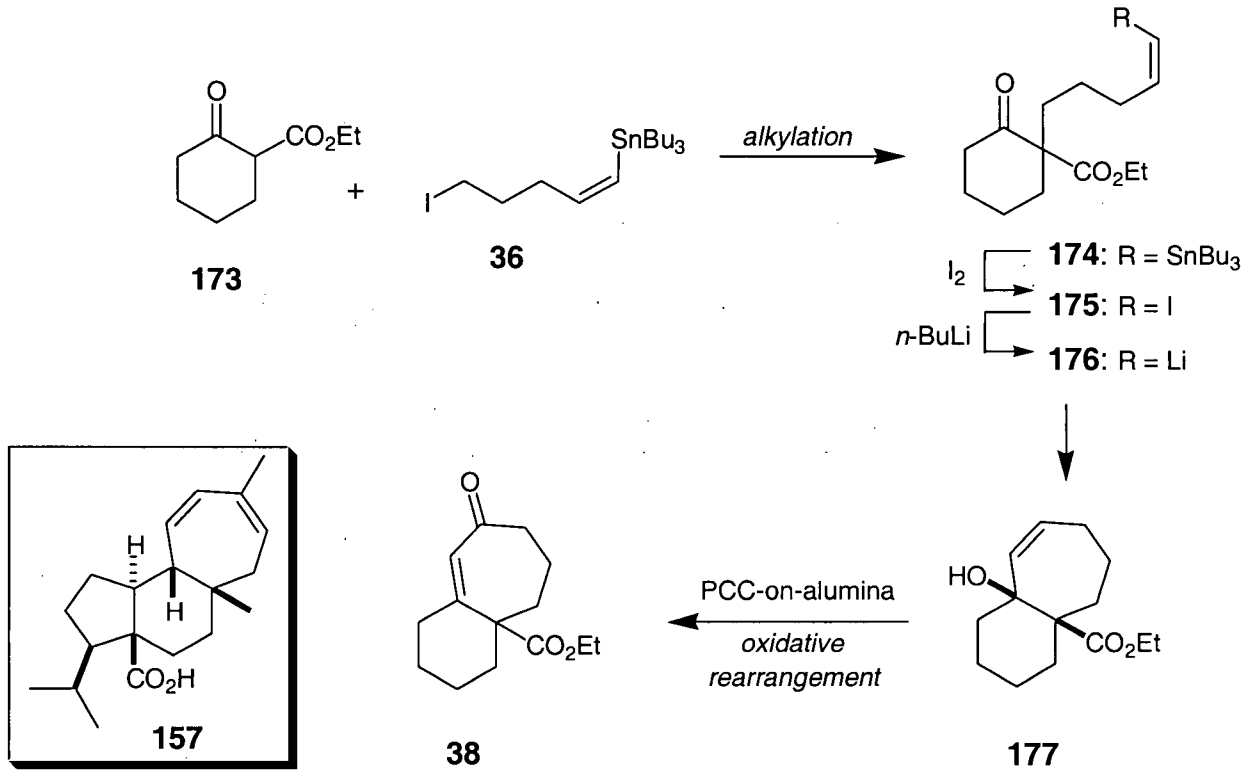


39 **152** **157**

Scheme 3.2: Retrosynthesis of isomulinic acid to mulin-11,13-dien-20-oic acid

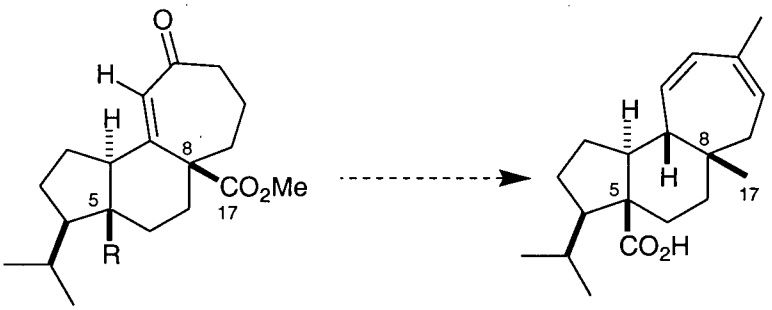
It is clear that part of the mulinane carbocyclic framework could potentially be prepared through the use of the seven-membered ring annulation procedure recently developed in this laboratory. Piers *et al.*[34] have shown that compounds such as bicycle **38** can be prepared from the bifunctional reagent *cis*-5-iodo-1-tri-*n*-butylstannylpent-1-ene (**36**) and a suitable keto ester, such as **173,** in four steps. Indeed, the bicyclic structure of **38** maps well onto mulin-11,13-dien-20-oic acid (**157**, **Scheme 3.3**). Alkylation of keto ester **173** with bifunctional reagent **36** yields compound **174**. The

alkenylstannane group is transformed into the corresponding alkenyl iodide upon treatment with iodine. A BuLi promoted lithium-iodine exchange[105] results in the formation of alkenyllithium **176**, which undergoes an intramolecular cyclization to furnish tertiary-allylic alcohol **177** after a suitable work-up procedure. Treatment of **177** with PCC-on-alumina causes an oxidative rearrangement[69-72] which yields enone **38** (see **Scheme 2.24**).



Scheme 3.3: Preparation of enone 38 using bifunctional reagent 36[34]

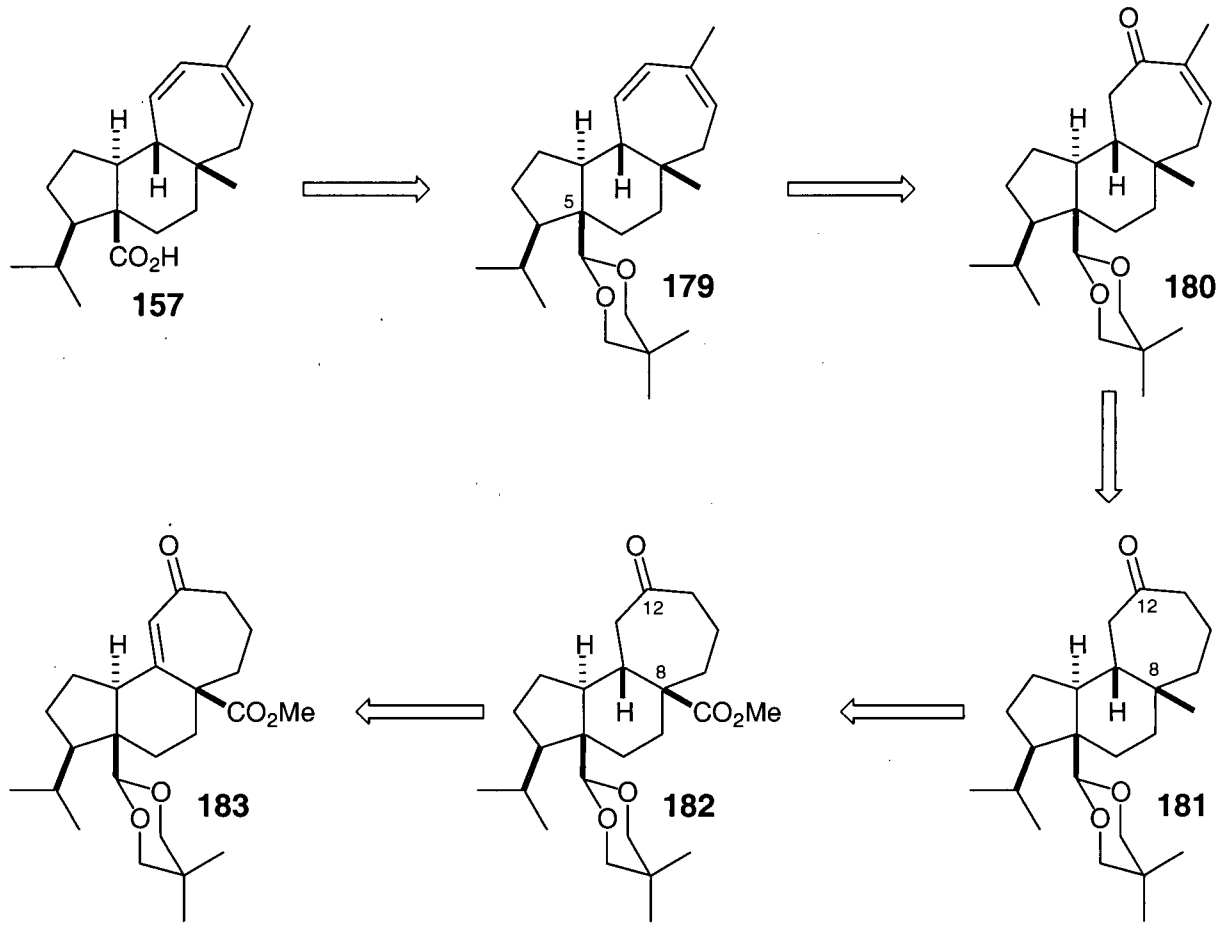
Having decided to make use of the bifunctional reagent *cis*-5-iodo-1-tri-*n*-butylstannylpent-1-ene (**36**) to construct the seven-membered ring of the mulinane diterpenoids, the task then becomes the elaboration of a suitable material such as **178** to mulin-11,13-dien-20-oic acid (**157, Scheme 3.4**). Note that the presence of a methoxycarbonyl group on C-8 of **178** precludes the use of this functional group as a surrogate for the carboxylic acid function on C-5 of the natural product. Three synthetic issues must then be resolved: 1) adjustment of the oxidation state of C-17, 2) use of a suitable functional group at C-5 and its transformation to a carboxylic acid moiety, and 3) preparation of the seven-membered ring diene from the seven-membered ring enone.



178 **157**

Scheme 3.4: Late stages of the synthetic problem

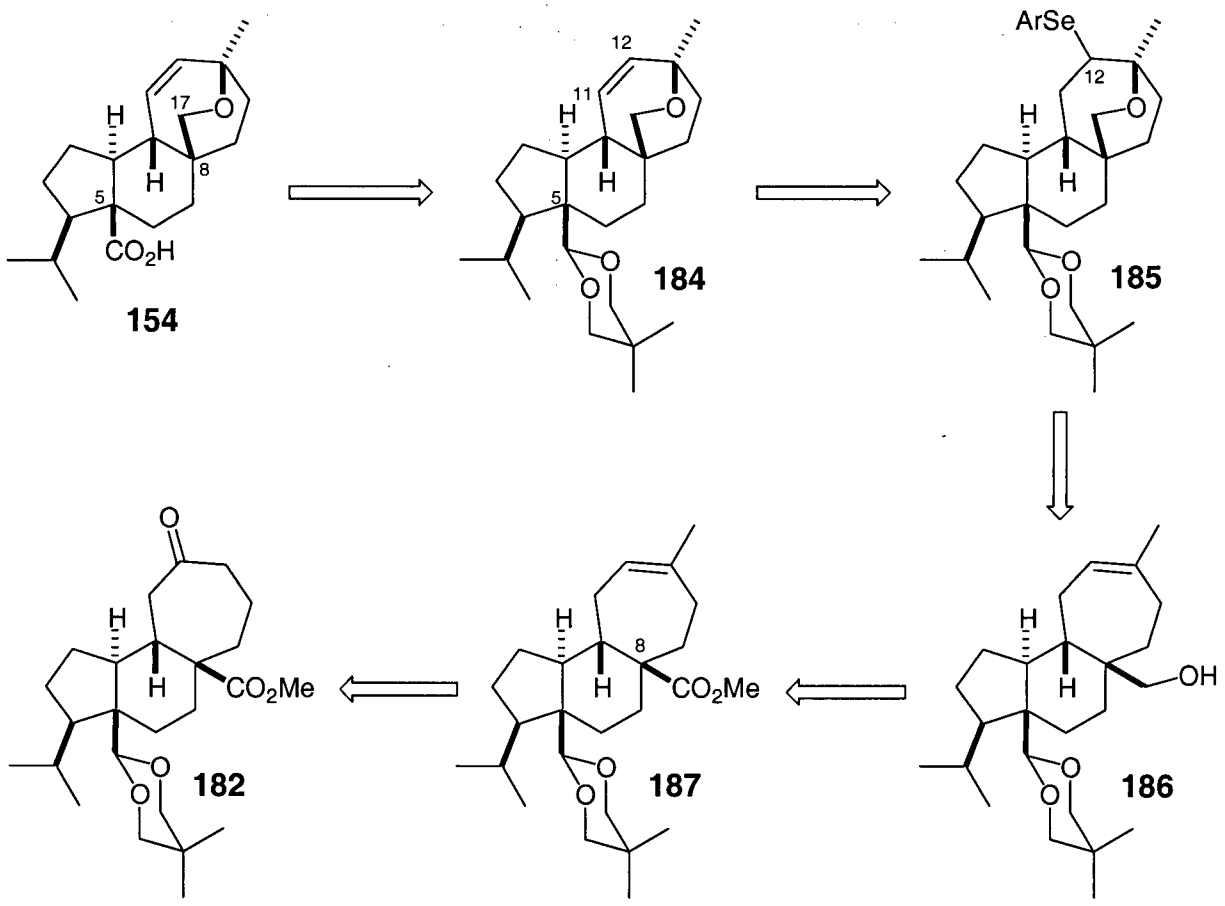
It appeared reasonable to use an acetal moiety at C-5 as a surrogate for the carboxylic acid moiety (**Scheme 3.5**). Thus, preparation of the carboxylic acid would likely involve an acid catalyzed deprotection of the aldehyde, followed by oxidation to the corresponding acid, and would occur at a late stage in the synthesis (**179** to **157**).



Scheme 3.5: Retrosynthesis of mulin-11,13-dien-20-oic acid to enone 183

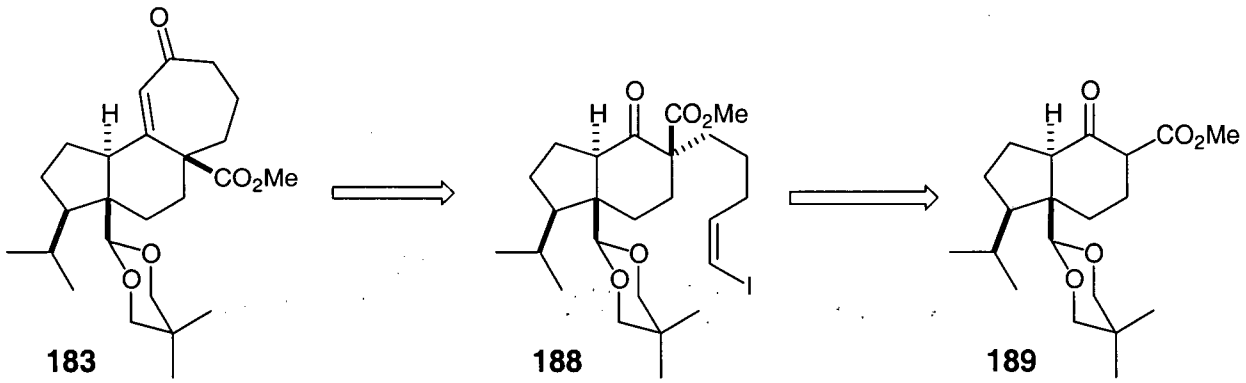
Preparation of the diene on the seven-membered ring of **179** should be possible from enone **180**. This material, in turn, should be accessible from ketone **181** using standard methods. In principle, the methyl group on C-8 (**181**) can be derived from the corresponding methyl carboxylate (**182**). It was recognized that this transformation (**182** to **181**) would potentially require protection of the ketone function at C-12. Finally, it was hoped that the *cis*-fusion between the six- and seven-membered rings would be established through the direct hydrogenation of enone **183**. Alternatively, the allylic alcohol obtained from the reduction of enone **183** could be used to direct the hydrogenation of the double bond under homogenous conditions.[106,107]

The presence of the methyl carboxylate moiety on C-8 may at first seem problematic. However, it must be noted that it imparts flexibility to this synthetic strategy. Indeed, a retrosynthetic analysis of mulinenic acid (**154**), which is oxygenated at C-17, reveals that it could potentially be derived from ketone **182** (**Scheme 3.6**). As mentioned earlier, the acetal moiety on C-5 should provide access to the carboxylic acid function of **154**. The double bond between C-11 and C-12 could be established through oxidation of the arylselenide moiety at C-12 of compound **185**, followed by thermolysis of the resulting selenoxide.[108] The etherification reaction leading to **185** from alcohol **186** would occur under the action of phenylselenenyl chloride as shown by Nicolaou *et al.*[109] or *N*-phenylselenophthalimide as demonstrated by Kuhnert and Maier.[110] Preparation of alcohol **186** would require the reduction of the methoxycarbonyl group at C-8. Finally, alkene **187** should be accessible from ketone **182** using standard methods.



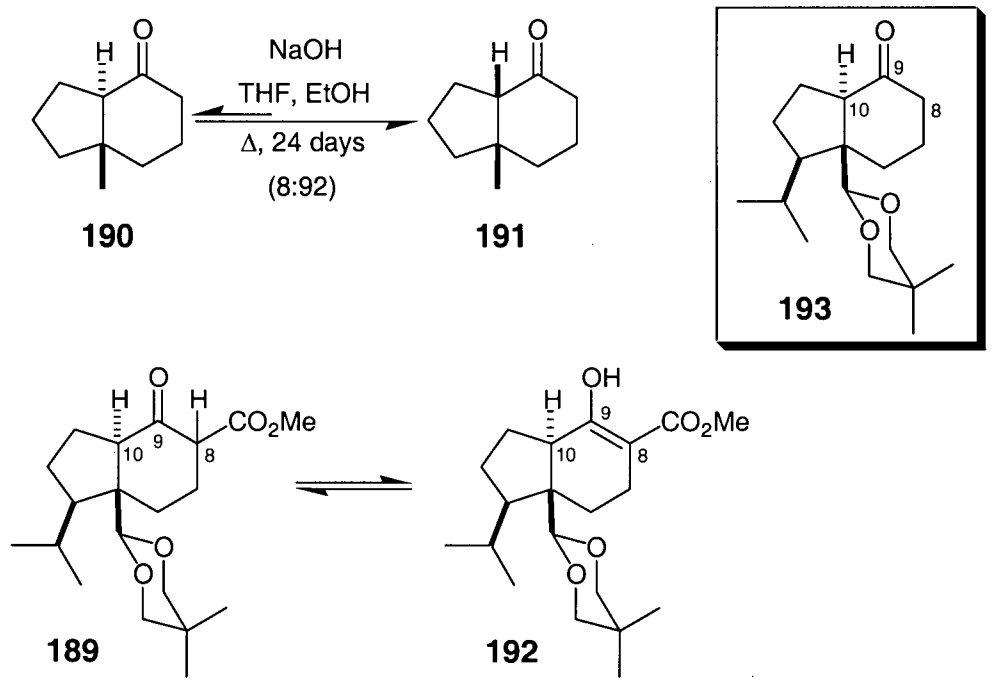
Scheme 3.6: Retrosynthetic analysis of mulinenic (154) acid to ketone 182.

It was expected that the annulation method described in **Scheme 3.3** would yield access to the pivotal enone (**183**). This process would require alkylation of keto ester **189** with *cis*-5-iodo-1-tri-*n*-butylstannylpent-1-ene (**36**) as shown in **Scheme 3.7**.



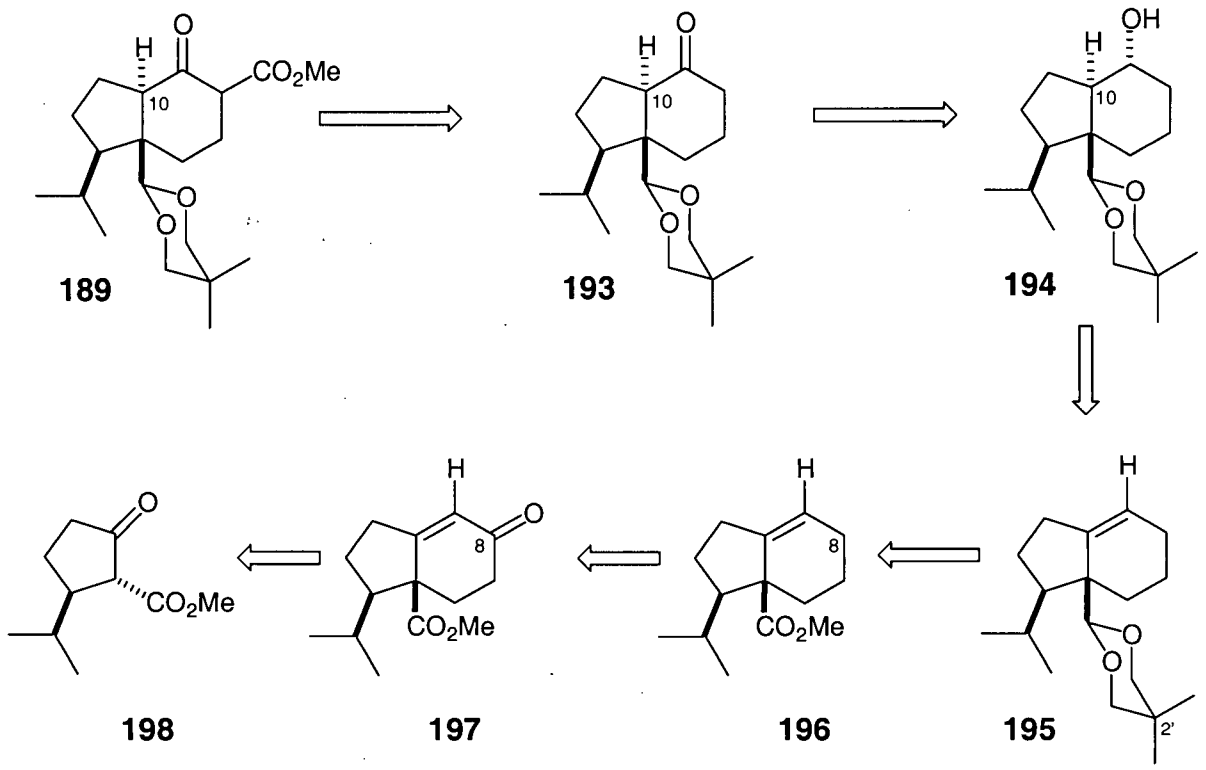
Scheme 3.7: Retrosynthesis of enone 183 to ketoester 189

The planned use of keto ester **189** requires some comment. It is well known that the relative energy of *cis*- and *trans*-fused hydrindane systems depends largely on their substitution pattern.[111] Dana and Lo Cicero[112] have shown that hydrindanone systems similar to ketone **193** (**Scheme 3.8**) exist in dynamic equilibrium as a mixture of epimers under equilibrating conditions. The example illustrated in **Scheme 3.8** indicates that ketone **193** could be susceptible to epimerization at C-10 in basic or acidic media. In principle, keto ester **189** should enolize as depicted in **192** (**Scheme 3.8**) and, as a result, should prevent epimerization at C-10.



Scheme 3.8: Dynamic equilibrium between ketones 190 and 191,[112] structure of ketone 193, and keto and enol forms of keto ester 189.

It was expected that keto ester **189** would be accessible from ketone **193** through the use of Mander's method[113] (**Scheme 3.9**). Oxidation of alcohol **194** under neutral conditions should provide access to ketone **193** without epimerizing the carbon chirality center at C-10. It was envisioned that a diastereoselective hydroboration reaction of alkene **195** would furnish alcohol **194** as the major product. It was postulated that the bulky 2',2'-dimethylpropylene acetal moiety of alkene **195** would impart a large degree of facial selectivity during the hydroboration event. Reduction of the ester moiety of **196** to the corresponding aldehyde, and subsequent protection of the aldehyde as the dimethylpropylene acetal would provide alkene **195**. The reduction of the carbonyl group at C-8 of **197** to a methylene group was expected to occur through formation of the corresponding dithioethylene ketal, followed by desulfurization with Raney nickel. Bicyclic enone **197** should be accessible from keto ester **198** through the use of a Robinson annulation. The preparation of keto ester **198** from inexpensive materials has been described in the literature.[114]

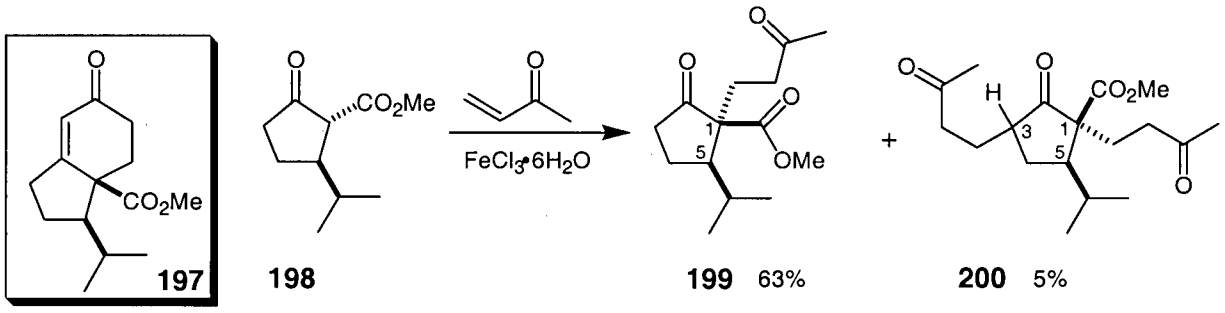


Scheme 3.9: Retrosynthesis of ketone 183 to ketoester 198

3.4.2.2 First synthetic approach to (±)-isomulinic acid

The proposed synthesis of (±)-isomulinic acid (**39**) required an efficient preparation of bicyclic enone **197** from keto ester **198**. It was expected that this task would be accomplished through a Robinson annulation. Unfortunately, attempts to carry out this transformation in one step were not successful and, as a result, a three step synthesis was devised.

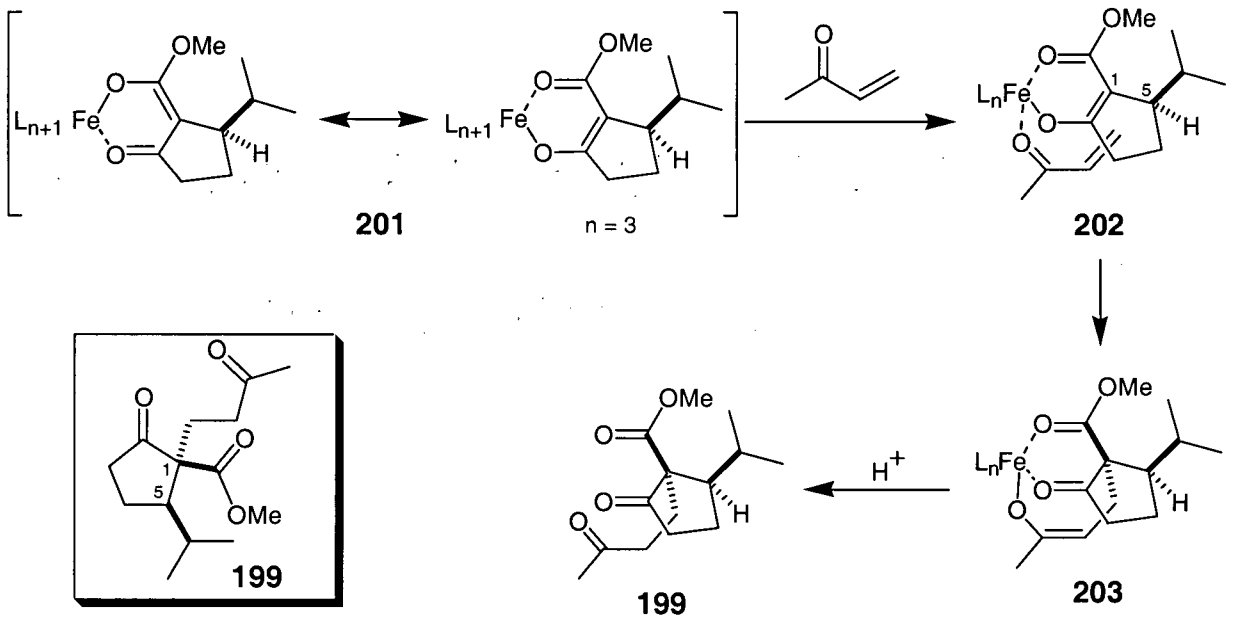
The alkylation of keto ester **198** with methyl vinyl ketone could be carried out in small scale using triflic acid as a catalyst as shown by Kotsuki *et al.*[115] Unfortunately, formation of a number of side products was observed when more than 3 mmol of keto ester **198** were used. The desired alkylation could also be carried out under the influence of an Fe(III) catalyst as demonstrated by Christoffers[116] (**Scheme 3.10**). Gratifyingly, this reaction could be carried out in large scale (162 mmol) and did not suffer from extensive formation of undesired products. Indeed, dione **199** was obtained in 63% yield and the major side-product (**200**) was isolated in only 5% yield. Some of the starting material (18%) was also recovered.



Scheme 3.10: Synthesis of dione 199

This alkylation reaction is thought to occur through the initial formation of a stable octahedral complex (**201**) in which the enolate of keto ester **198** behaves as a resonance stabilized ligand (**Scheme 3.11**). Methyl vinyl ketone then coordinates to complex **201** to form intermediate **202**. Note that although methyl vinyl ketone may approach the metal center from either side of the chelating ligand, the alkylation at C-1 occurs preferentially *anti* to the isopropyl group at C-5 for steric reasons. As a result the correct relative configuration is established at C-1 and C-5 of dione **199**. Note also

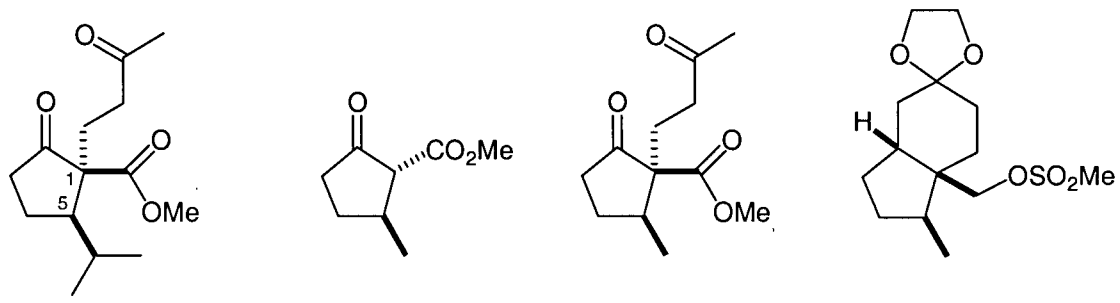
that methyl vinyl ketone must adopt an S-*cis* configuration in order for the alkylation to occur. Complex **203** is destabilized relative to complex **202** and, as a result, the ligand is released.



Scheme 3.11: Pathway for the Fe(III) mediated alkylation of keto ester 198

The spectral data collected on dione **199** was in full accord with the assigned structure. The IR spectrum clearly showed three strong absorptions at 1749 cm^{-1}, 1731 cm^{-1} and 1718 cm^{-1}, which account for the carbonyl functions in the molecule. In addition, the ^{13}C NMR spectrum contained an ester carbonyl resonance at $\delta = 171.0$ and two ketone carbonyl resonances at $\delta = 207.9$ and 216.5. The ^{1}H NMR spectrum contained the correct number of signals, including a three proton singlet at $\delta = 2.08$ corresponding to the methyl ketone function. Finally, an HRMS measurement of the parent ion was consistent with the molecular formula of the desired dione.

The relative configuration at C-1 and C-5 could not be verified spectroscopically. However, the assigned relative configuration was supported by literature precedent. Indeed, Coates has shown that the analogous diketone **205** could be obtained from keto ester **204**. Diketone **205** was converted to mesylate **206**, the structure of which was determined by X-ray crystallography (see **Figure 3.8**).[117]

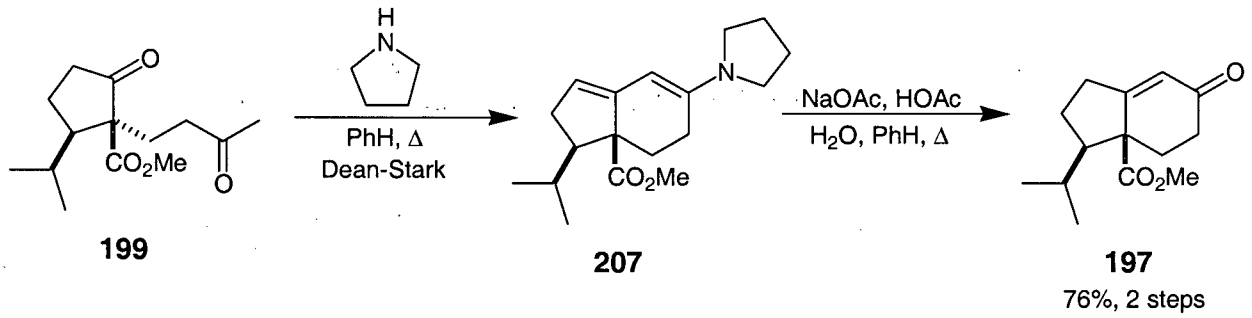


199 **204** **205** **206**

Figure 3.8: Structures of compounds 199, 204, 205 and 206[117]

The major side product formed during the alkylation of keto ester **198** was determined to be trione **200** based on the spectral data collected. Indeed, both the ^{1}H NMR and ^{13}C NMR spectra contained the correct number of signals. The ^{13}C NMR spectrum contained signals at δ = 171.4, 207.8, 210.7 and 216.6, which account for the four carbonyl groups in the molecule. The ^{1}H NMR spectrum showed two methyl singlets at δ = 2.13 and 2.17, which account for the two methyl ketone carbonyl functions. The IR spectrum displayed three carbonyl resonances at 1747, 1730 and 1716 cm^{-1}. Moreover, the molecular mass of **200** was confirmed by an HRMS measurement of its parent ion. The relative configuration of the carbon chirality center at C-3 of trione **200** was not determined.

The next step in the sequence involved a classical aldol condensation-dehydration sequence to form bicyclic enone **197**. A review of the literature suggested the use of Scanio and Hill's method.[118] Thus, reaction of dione **199** with pyrrolidine led to the formation dienamine **207** upon removal of water (**Scheme 3.12**). This material could not be fully characterized since it decomposed readily upon contact with silica gel. However, a GC-LRMS analysis indicated that the molecular mass of the major component of the crude mixture did indeed correspond to the expected dienamine. Compound **207** was hydrolyzed using the method devised by Johnson *et al.*[119] to furnish the desired enone (**197**).



199 **207** **197**

76%, 2 steps

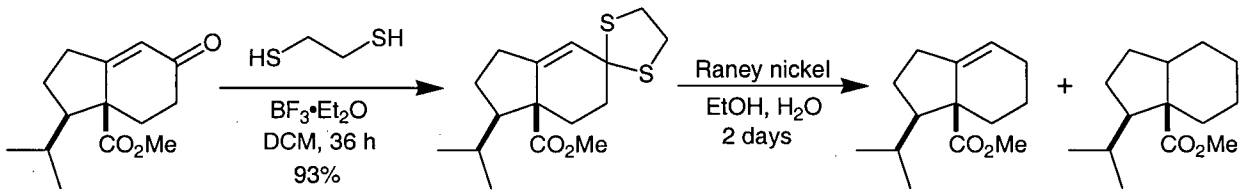
Scheme 3.12: Synthesis of enone 197

The spectral data collected on enone **197** was in full accord with the assigned structure. The IR spectrum showed a resonance at 1664 cm^{-1}, which was attributed to the α,β-unsaturated ketone moiety. The ^{1}H NMR spectrum displayed a one-proton singlet at $\delta = 5.81$ corresponding to the alkenyl proton. The ^{13}C NMR spectrum showed an alkenyl signal at $\delta = 123.4$ corresponding to the unsaturated carbon at the position α to the ketone. Two signals at $\delta = 171.2$ and 172.3 accounted for the ester carbonyl carbon and the unsaturated carbon at the β position of the ketone. A signal observed at $\delta = 198.8$ was assigned to the enone carbonyl carbon. An HRMS measurement of the parent ion was consistent with the molecular formula of the desired product.

With an efficient synthesis of a bicyclic compound which possesses the correct relative configuration at C-3 and C-5 (mulinane numbering), the stage was set to prepare alkene **195**. The reduction of the ketone carbonyl of enone **197** to a methylene group was achieved using a two-step sequence. Formation of dithioketal **208** was accomplished efficiently upon treatment of enone **197** with an excess of 1,2-ethanedithiol and a catalytic amount of $BF_3 \bullet Et_2O$ in DCM (**Scheme 3.13**).

The structure of dithiane **208** was verified by inspection of its spectral data. The IR spectrum showed a single carbonyl resonance at 1718 cm^{-1} corresponding to the ester carbonyl group. Both the ^{13}C NMR and ^{1}H NMR spectra displayed the correct number of signals. The carbonyl resonance observed at $\delta = 198.8$ in enone **197** was notably absent in the ^{13}C NMR spectrum of dithiane **208**. An HRMS measurement of the parent ion confirmed the molecular formula of **208**.

The reduction of the dithiane function of **208** to a methylene group occurred under the action of Raney nickel (**Scheme 3.13**). Unfortunately, this desulfurization took place at a slow rate and in modest yield. A GC-LRMS trace indicated that the major product was the desired alkene and that some over-reduction to the saturated bicycle (**209**) had also occurred. Luckily, the over-reduction process took place at a much slower rate than the desired desulfurization.

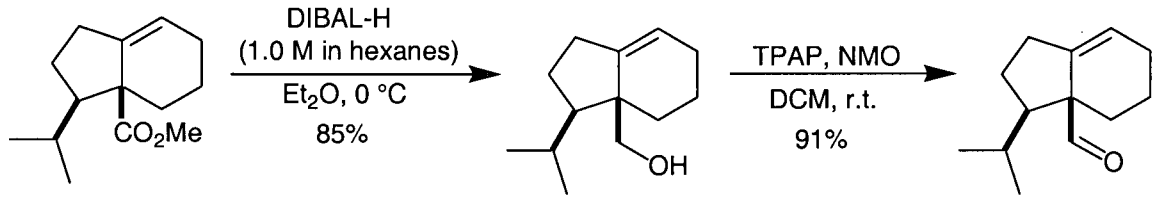


197 **208** **196** 66% **209** trace

Scheme 3.13: Synthesis of alkene 196

Alkene **196** displayed spectral data in accordance with the assigned structure. The ^{1}H NMR spectrum contained the correct number of signals, and the ^{13}C NMR spectrum showed 14 carbon resonances. A *J*-mod ^{13}C NMR experiment demonstrated that compound **196** contained five methylene groups, and a total of six methine and methyl groups. The IR spectrum was not particularly informative, but an HRMS measurement of the parent ion confirmed the molecular formula of alkene **196**.

Conversion of the ester moiety of compound **196** into an aldehyde was efficiently accomplished in two steps. Thus, treatment of alkene **196** with two equivalents of DIBAL-H resulted in the formation of the corresponding alcohol (**210**) in good yield (**Scheme 3.14**). The strong absorption at 3369 cm^{-1} was attributed to a hydroxyl OH stretching vibration. The three-proton singlet previously observed at $\delta = 3.63$ in the ^{1}H NMR spectrum of methyl ester **196** was notably absent. A two-proton multiplet that appeared at $\delta = 3.54\text{-}3.59$ in the ^{1}H-NMR spectrum was assigned to the carbinol protons of alcohol **210**. The signal occurring at $\delta = 64.9$ in the ^{13}C NMR spectrum was attributed to the carbinol carbon. Finally, a *J*-mod ^{13}C NMR experiment verified that the product contained six methylene groups, and an HRMS measurement of the parent ion verified the molecular formula of alcohol **210**.

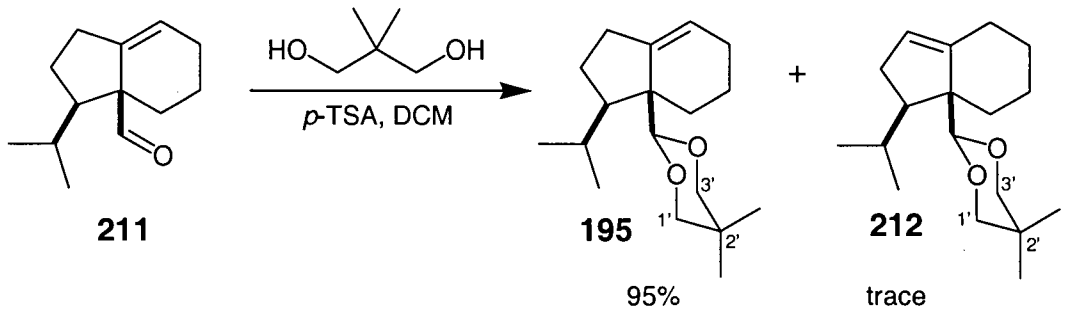


196 210 211

Scheme 3.14: Preparation of aldehyde 211

Alcohol **210** was oxidized to the corresponding aldehyde in excellent yield using Ley's method[88] (**Scheme 3.14**). The appearance of a singlet at $\delta = 9.65$ in the ^{1}H NMR spectrum served as evidence for the desired aldehyde. The carbonyl carbon was observed at $\delta = 203.2$ in the ^{13}C NMR spectrum. The IR spectrum displayed a strong carbonyl stretch resonance at 1718 cm^{-1}. Moreover, an HRMS measurement of the parent ion confirmed the molecular formula of aldehyde **211**.

The next task involved protection of the tertiary aldehyde moiety of **211** as a 2,2-dimethylpropylene acetal. This transformation was expected to occur through the use of an excess of 2,2-dimethylpropanediol and a catalytic amount of a suitable Brønsted acid (**Scheme 3.15**). It was recognized that migration of the double bond from the six-membered ring to the five-membered ring could occur under these conditions. In the event, the desired acetal (**195**) was obtained in good yield and was accompanied by small amounts of a side product in which the double bond had migrated to the five membered ring (as in **212**).

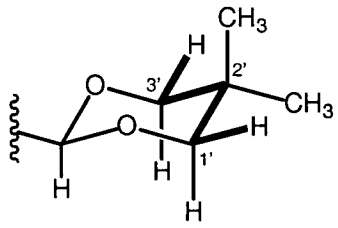


211 195 212

95% trace

Scheme 3.15: Preparation of acetal 195

Inspection of the ^{1}H NMR and ^{13}C NMR data collected on the major product made it clear that the aldehyde moiety had been converted to the corresponding acetal. The ^{13}C NMR spectrum showed a signal at $\delta = 103.4$ that was assigned to the acetal carbon atom, and two signals at $\delta = 77.4$ and 78.2 that were assigned to the C-1' and C-3' of the 2',2'-dimethylpropylene acetal moiety. The ^{1}H NMR spectrum displayed the diagnostic signals outlined in **Figure 3.9**. The long-range coupling (W-coupling) constant of 2.9 Hz allowed for the distinction between the equatorial and the axial protons.



equatorial protons
$\delta = 3.57$-3.62, dd, $J = 10.7, 2.9$ Hz
$\delta = 3.60$-3.65, dd, $J = 10.7, 2.9$ Hz

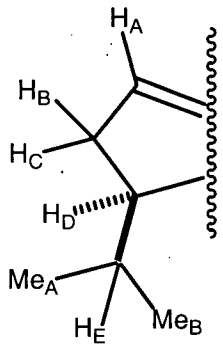
acetal proton
$\delta = 4.33$, s

axial protons
$\delta = 3.28$, d, $J = 10.7$ Hz
$\delta = 3.36$, d, $J = 10.7$ Hz

methyl groups
$\delta = 0.67$, s
$\delta = 1.16$, s

Figure 3.9: Diagnostic ^{1}H NMR data for the acetal moiety of 195

As indicated in **Scheme 3.15**, a second acetal could be isolated in very low yield from the reaction mixture. The spectral data collected on this material was very similar to that collected for acetal **195**. However, a 1D-TOCSY experiment demonstrated the presence of the spin system depicted in **Figure 3.10** and thus verified that this material was the isomerized alkene (**212**).



H_A: $\delta = 5.44$ (m)

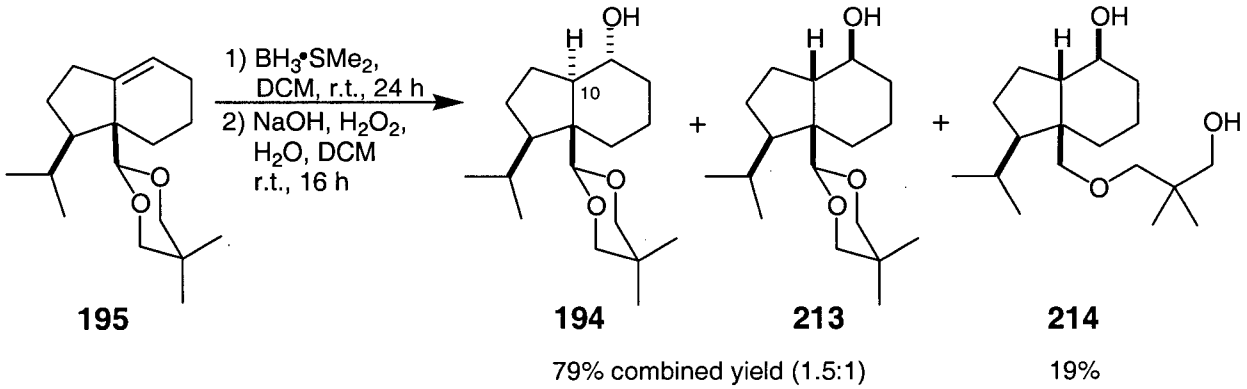
H_B, H_C, H_D and H_E { $\delta = 2.22$-2.30 (m, 1H); $\delta = 1.99$-2.12 (m, 2 H); $\delta = 1.43$-1.55 (m 1 H)

Me_A and Me_B { $\delta = 0.99$ (d, 3 H, $J = 6.4$ Hz); $\delta = 0.85$ (d, 3 H, $J = 6.6$ Hz)

irradiation of H_A enhances H_B, H_C, H_D, H_E, Me_A and Me_B

Figure 3.10: Spin system present in alkene 212 as determined using a selective 1D TOCSY experiment

With alkene **195** in hand, the stage was set for the hydroboration experiment that was expected to introduce the carbon chirality center at C-10 (mulinane numbering) with the correct relative configuration. A number of hydroborating agents were screened including BH_3•THF, BH_3•SMe_2, 9-BBN, catechol borane and catechol borane-$LiBH_4$. These preliminary experiments demonstrated that the best results were obtained using BH_3•SMe_2 as the hydroborating reagent in DCM. A mixture of alcohols **194** and **213** (see **Scheme 3.16**) was invariably obtained. However, the composition of the mixtures and the total yield of the two alcohols (**194** and **213**) varied. An examination of the more polar material derived from the hydroboration-oxidation reaction revealed that diol **214** was the major side product.

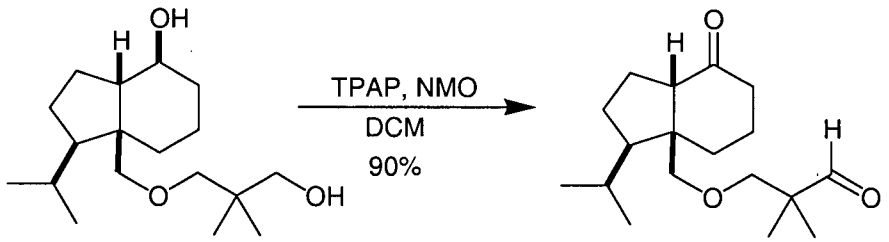


Scheme 3.16: Hydroboration and oxidation of alkene 195

The mixture of alcohols **194** and **213** was easily separated from diol **214** using flash column chromatography on silica gel. Diol **214** displayed two three-proton singlets at δ = 2.11 and δ = 2.20 in the ^{1}H NMR spectrum. The diagnostic signals corresponding to the acetal moiety (see **Figure 3.9**) were notably absent. The ^{13}C NMR spectrum displayed signals at δ = 71.0, 71.5, 75.4 and 80.4, which account for all four carbon atoms bonded to oxygen. The IR spectrum clearly showed the expected absorbance at 3370 cm^{-1}. Finally, an HRMS measurement of the parent ion confirmed its molecular formula.

The structure of diol **214** was further confirmed by its oxidation[88] to the corresponding keto aldehyde (**215**, **Scheme 3.17**). This material exhibited two distinct

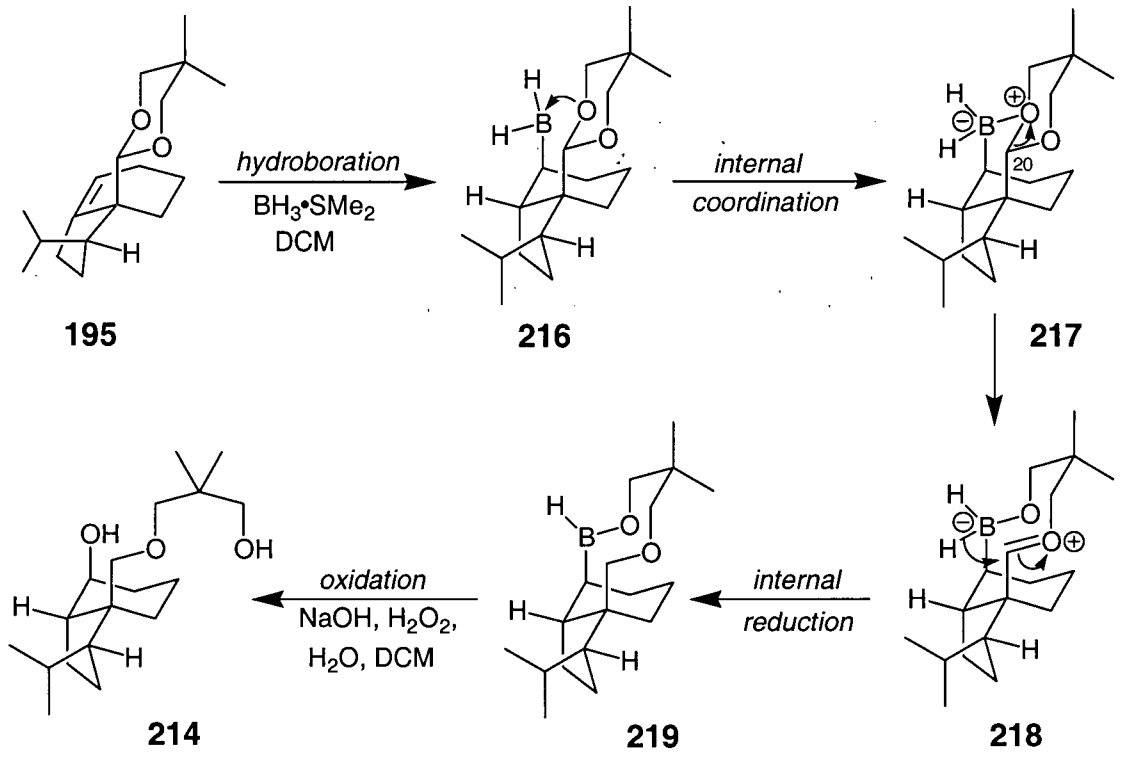
AB spin systems in its ^{1}H NMR spectrum, which can be assigned to the two methylene groups flanking the ether oxygen atom. In addition, a singlet at δ = 9.51 indicated the presence of the expected tertiary aldehyde. The ^{13}C NMR spectrum showed two carbonyl signals at δ = 213.8 and δ = 204.9 which can be assigned to the ketone and aldehyde carbonyl carbons, respectively. The IR spectrum of this material displayed two strong absorptions at 1707 cm^{-1} and 1729 cm^{-1} which also indicated the presence of a ketone and an aldehyde carbonyl. Finally, an HRMS measurement of the parent ion was consistent with the molecular formula of keto aldehyde **215**.



214 **215**

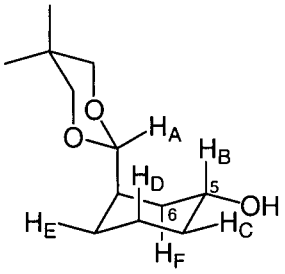
Scheme 3.17: Oxidation of diol 214 to keto aldehyde 215

The fact that no isomers of diol **214** were isolated indicates that the reductive opening of the acetal moiety occurred in an intramolecular fashion. A postulated mechanism for this side reaction is presented in **Scheme 3.18**. Thus, after initial hydroboration of alkene **195** to provide the *cis*-fused borane derivative (**216**), one of the oxygen atoms on the acetal group can coordinate to the boron atom to form ylide **217**. The juxtaposition of the activated acetal carbon and the borohydride moiety allows for the internal reduction of C-20 (mulinane numbering) to form intermediate **218**. Oxidation of the borane (**219**) results in formation of the observed diol (**214**).



Scheme 3.18: Proposed mechanism for the formation of diol 214

Although alcohols **194** and **213** were difficult to separate by flash column chromatography, a small amount of the *trans*-fused alcohol (**194**) was purified and its structure was fully assigned based on extensive NMR experiments. The relative configuration of the two newly introduced carbon chirality centers at C-5 and C-6 was confirmed through a number of selective NOE difference experiments as shown in **Figure 3.11**.



partial structure of alcohol **194**

H_A: δ = 4.25 (s)
signal is enhanced by irradiation of H_B and H_E

H_B: δ = 4.10-4.17 (ddd, *J* = 10, 10, 5 Hz)
signal is enhanced by irradiation of H_A and H_C

H_C: δ = 1.96-2.04 (m)
signal is enhanced by irradiation of H_B

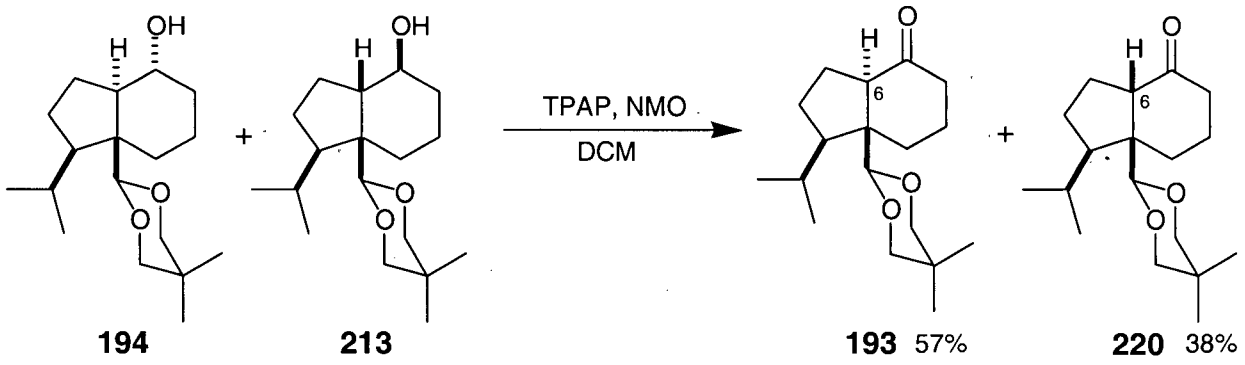
H_D: part of a multiplet at δ = 1.74-1.91
signal is enhanced by irradiation of H_A and H_B

H_E: δ = 2.41-2.50 (ddd, *J* = 13.0, 3.0, 3.0 Hz)
signal is enhanced by irradiation of H_A

H_F: part of a multiplet at δ = 1.23-1.48
signal **is not** enhanced by irradiation at H_A or H_B

Figure 3.11: Selected NOE difference data observed for alcohol 194

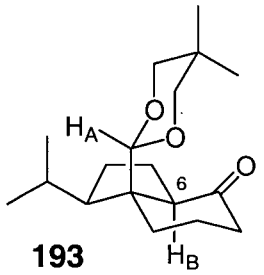
In view of the tedious separation of alcohols **194** and **213**, it was decided to carry out an oxidation[88] of the mixture (**Scheme 3.19**). It was gratifying to find that the mixture of the corresponding ketones (**193** and **220**) could be easily separated by flash column chromatography on silica gel.



Scheme 3.19: Oxidation of alcohols 194 and 213 to ketones 193 and 220

Ketone **193** exhibited a strong carbonyl absorption at 1708 cm^{-1}. In addition, its molecular formula was confirmed through an HRMS measurement of its parent ion. A resonance at δ = 210.7 in the ^{13}C NMR spectrum confirmed the presence of a ketone carbonyl. Although, the structure of ketone **193** could be fully assigned, no conclusive evidence regarding the relative configuration of the carbon chirality center at C-6 could

be obtained. However, in a selective NOE difference experiment, irradiation of the acetal proton did not enhance the signal corresponding to the proton at C-6 (see **Figure 3.12**). This result indicated that ketone **193** was likely the desired *trans*-fused product.



193

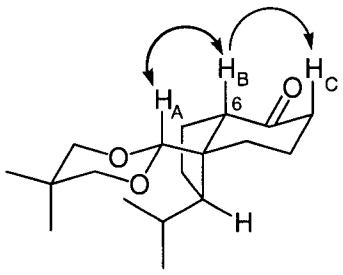
H_A: δ = 4.15 (s)

H_B; δ = 2.11-2.18 (dd, *J* = 12.0, 7.3 Hz)

irradiation of H_A **does not** enhance H_B

Figure 3.12: Selected NOE difference data observed for ketone 193

The *cis*-fused ketone (**220**) displayed a strong carbonyl resonance at 1708 cm^{-1}. An HRMS measurement of the parent ion verified the molecular formula. A signal at δ = 214.4 in the ^{13}C NMR spectrum demonstrated the presence of a ketone carbonyl. In order to confirm the conclusions regarding the newly introduced carbon chirality center, a full suite of NMR experiments were performed on ketone **220** and its structure was fully assigned. A number of selective NOE difference experiments performed on ketone **220** confirmed the relative configuration at C-6 (**Figure 3.13**).



220

H_A: δ = 4.27 (s)
signal is enhanced by irradiation of H_B

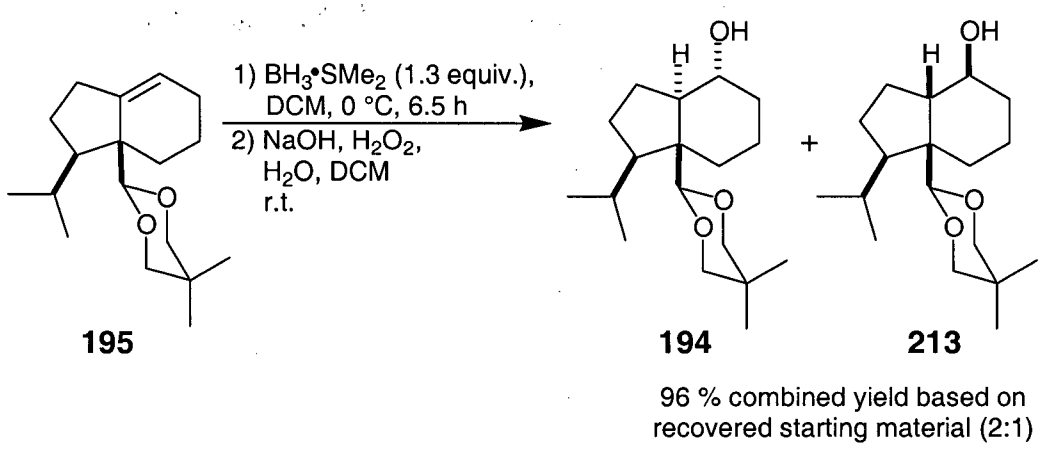
H_B: δ = 2.86-2.93 (dd, *J* = 7.5, 7.5 Hz)
signal is enhanced by irradiation of H_A

H_C: δ = 2.14-2.24 (ddd, *J* = 14.7, 8.3, 3.1 Hz)
signal is enhanced by irradiation of H_B

Figure 3.13: Selected NOE difference data observed for ketone 217

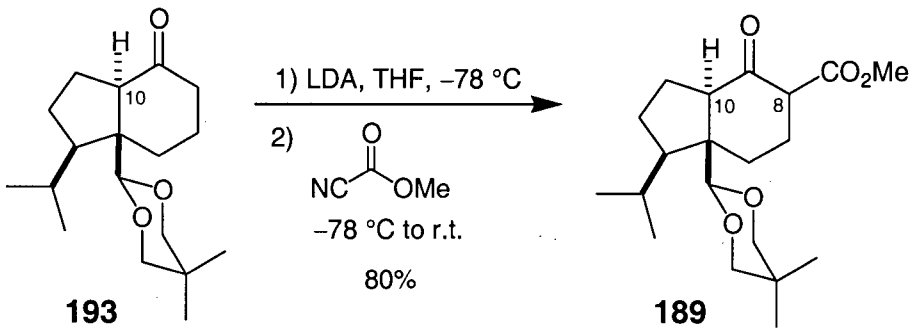
As indicated in **Scheme 3.16**, the hydroboration-oxidation sequence leading to alcohols **194** and **213** was not very selective and required optimization. To this end, a series of experiments were carried out in which the reaction solvent (Et_2O, pentane,

DCM and THF), reaction temperature (0 °C, 10 °C and r.t.) and the amount of hydroborating agent (1.3 and 10 equivalents of BH_3•SMe_2) were varied. **Scheme 3.20** shows the best conditions found in small scale reactions (0.23 mmol of alkene **195**). Similar results were observed when the reaction was scaled up (see experimental section for details).



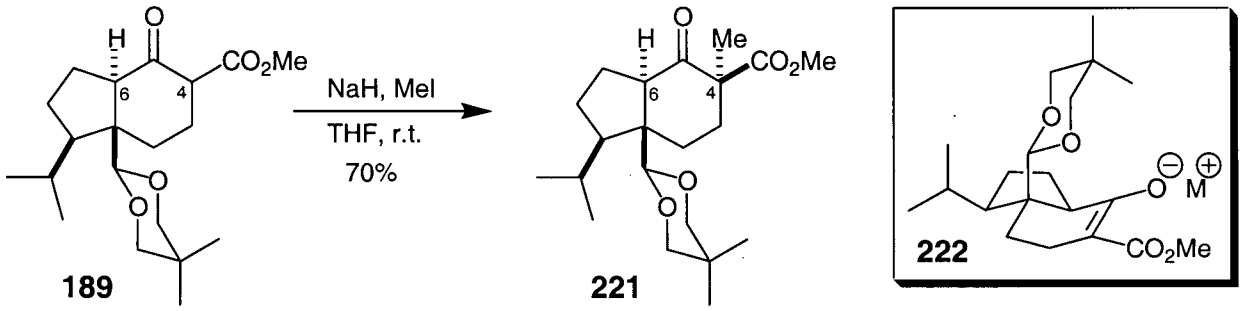
Scheme 3.20: Optimized conditions for the hydroboration of alkene 195 to alcohol 194

With access to sufficient amounts of ketone **193**, it became possible to explore the preparation of keto ester **189**. The installation of the methoxycarbonyl moiety was efficiently accomplished using the method developed by Mander[113] (**Scheme 3.21**). Unfortunately, characterization of the keto ester proved difficult. TLC analysis of the reaction mixture indicated the presence of two products. Inspection of the ^1H NMR spectrum indicated that the compound existed as a mixture of isomers



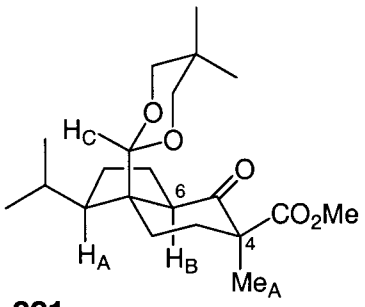
Scheme 3.21: Preparation of keto ester 189

According to the synthetic plan, keto ester **189** was to be alkylated with the bifunctional reagent *cis*-5-iodo-1-tri-*n*-butylstannylpent-1-ene (**36**, see **Scheme 3.3** and **Scheme 3.7**). It was decided to probe the stereochemical outcome of the alkylation process using methyl iodide as the electrophile (**Scheme 3.22**). Recall that this reaction was expected to establish the new carbon chirality center at C-8 (mulinane numbering) with the correct relative configuration. Thus, the alkylation of enolate **222** should proceed to give the axial methyl group based on stereoelectronic[120] grounds. In the event, alkylation of keto ester **189** furnished keto ester **221** as a single product.



Scheme 3.22: Stereoselective alkylation of keto ester 189

Compound **221** exhibited a three-proton singlet at $\delta = 1.40$ in the ^{1}H NMR spectrum corresponding to the newly introduced methyl group. The methyl ester moiety was observed as a three-proton singlet at $\delta = 3.69$ in the ^{1}H NMR spectrum. In addition, the ester carbonyl group gave rise to a signal at $\delta = 174.3$ in the ^{13}C NMR spectrum. Due to a fortuitous dispersion of signals in the ^{1}H NMR spectrum, the structure of keto ester **221** could be fully assigned. A set of one dimensional NOE difference experiments verified the relative configuration at C-4 and C-6 (**Figure 3.14**). Note that these experiments also serve to indirectly prove the structure of keto ester **189**.



221

H_A: δ = 1.28-1.36 (ddd, J = 9.4, 9.4, 9.4 Hz)
signal is enhanced by irradiation of H_B

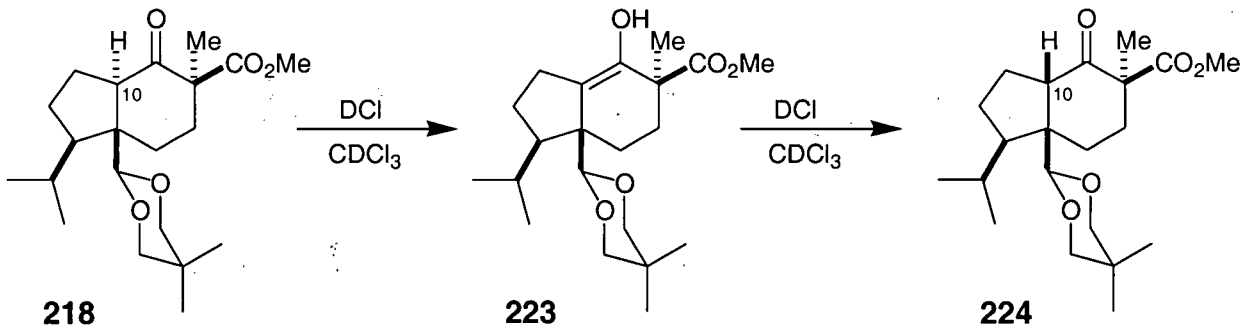
H_B: δ = 2.38-2.43 (dd, J = 11.8, 7.2 Hz)

H_C: δ = 4.20 (s)
signal **is not** enhanced by irradiation of H_B

Me_A: δ = 1.40 (s)
signal is enhanced by irradiation of H_B

Figure 3.14: Selected NOE difference data for ketoester 221

Although keto ester **221** could be synthesized with the correct relative configuration at C-3, C-5, C-8 and C-10 (mulinane numbering), it was recognized that this material was susceptible to epimerization at C-10 (mulinane numbering). Indeed, the sample used to obtain the NMR data for compound **221** had already begun to epimerize to keto ester **224** in the NMR tube, presumably through the enolization of the ketone group under the action of trace amounts of DCl to form enol **223** (**Scheme 3.23**).



218 223 224

Scheme 3.23: Epimerization of ketoester 218 to ketoester 221

This undesired epimerization indicated that the proposed intermediates **225** and **188** (**Figure 3.15**) would also be susceptible to epimerization, and would have to be used shortly after their preparation.

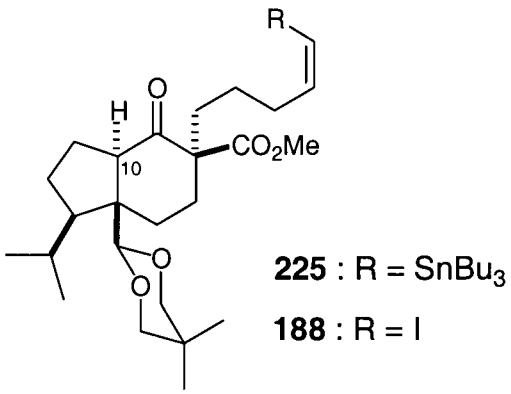
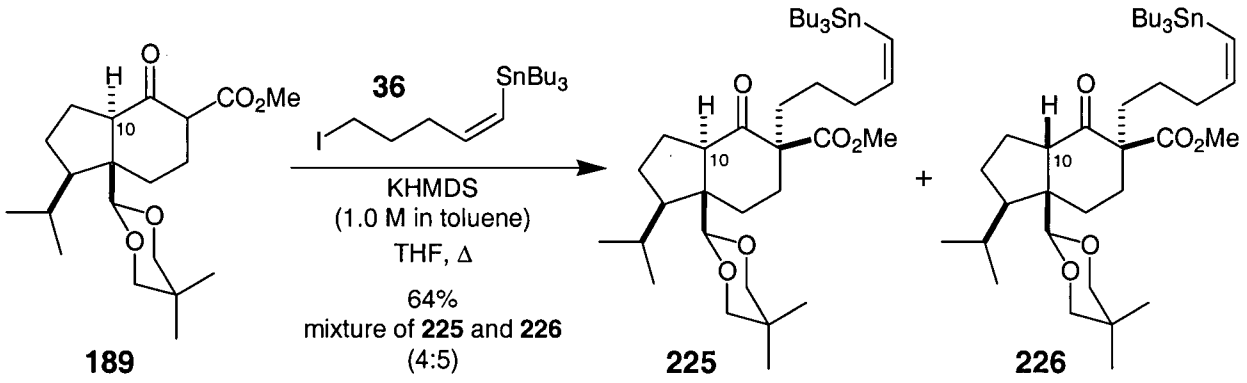


Figure 3.15: Proposed intermediates susceptible to epimerization

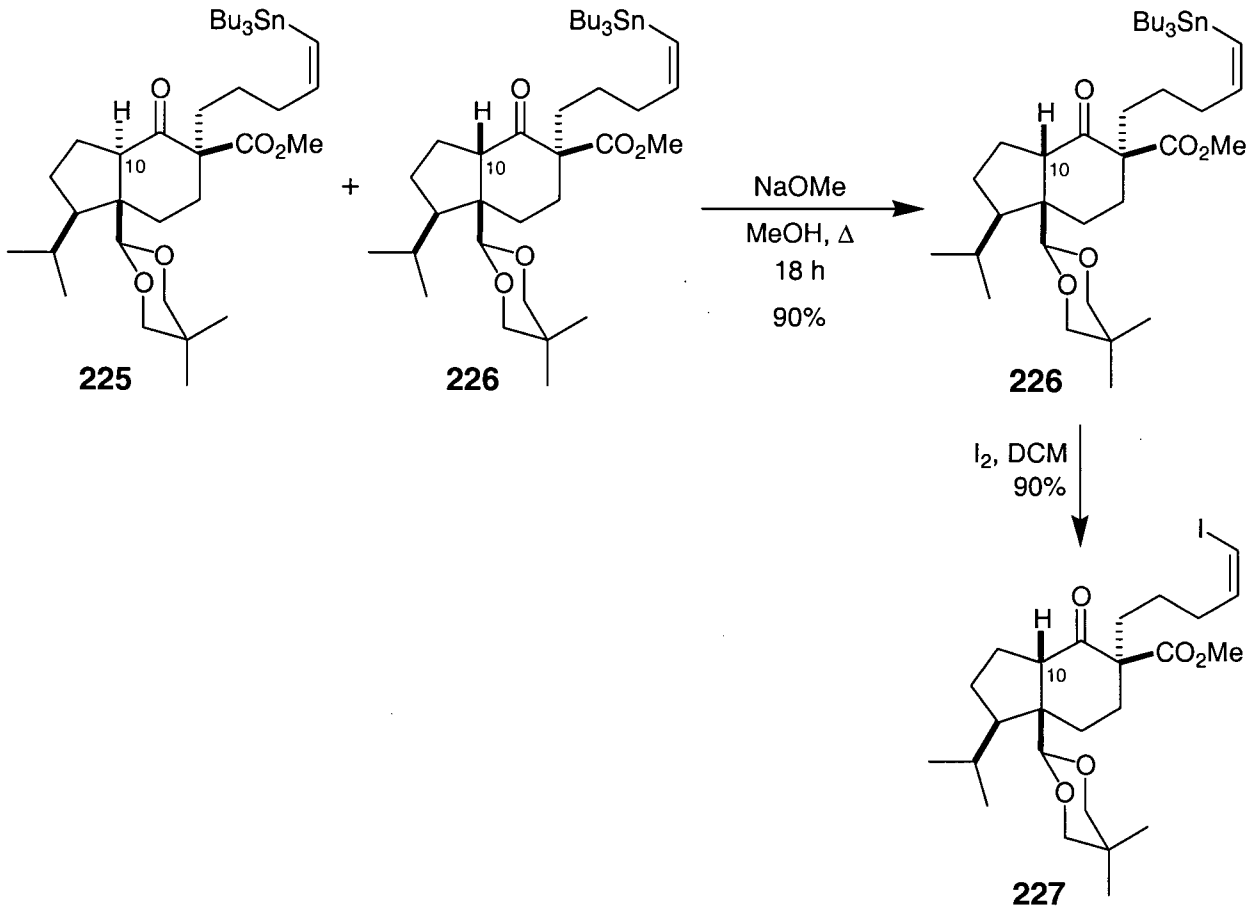
Surprisingly, the proposed alkylation of keto ester **189** with the bifunctional reagent *cis*-5-iodo-1-tri-*n*-butylstannylpent-1-ene (**36**) did not take place under the conditions outlined by Walker[121] or under the conditions used to prepare keto ester **221**. The use of KHMDS as the base led to an inseparable mixture of the desired ketoester (**225**) and its C-10 (mulinane numbering) epimer **226**. Initially it was thought that the observed epimerization resulted from deprotonation of keto ester **225** with excess base. However, a mixture of **225** and **226** was observed even when a deficiency of base was used. The reason(s) for the epimerization of **225** to **226** remain unclear.



Scheme 3.24: Alkylation of ketoester 189 with the bifunctional reagent *cis*-5-iodo-1-tri-*n*-butylstannylpent-1-ene (36)

The problems associated with separating keto ester **225** from its C-10 epimer (**226**) rendered it difficult to characterize. However, it could be shown that the mixture

of keto esters **225** and **226** converges to **226** exclusively upon treatment with base (**Scheme 3.25**). It could also be shown that keto ester **226** can be prepared as a single compound from ketone **220**. Alkenylstannane **226** was converted to alkenyl iodide **227** upon treatment with iodine.



Scheme 3.25: Preparation of alkenyl iodide 227

The spectral data collected on alkenyl iodide **227** verified its structure. The ^{1}H NMR spectrum displayed a two-proton multiplet at $\delta = 6.10\text{-}6.20$, which was assigned to the alkenyl protons. The ^{13}C NMR spectrum displayed two signals at $\delta = 82.8$ and 140.7 which were attributed to the vinyl iodide moiety. A *J*-mod ^{13}C NMR experiment demonstrated the presence of nine methylene groups and a total of eleven methyl and methine groups. The IR spectrum showed two carbonyl stretching absorptions at 1702 and 1736 cm^{-1}. The molecular mass of **227** was verified through an HRMS measurement of its parent ion.

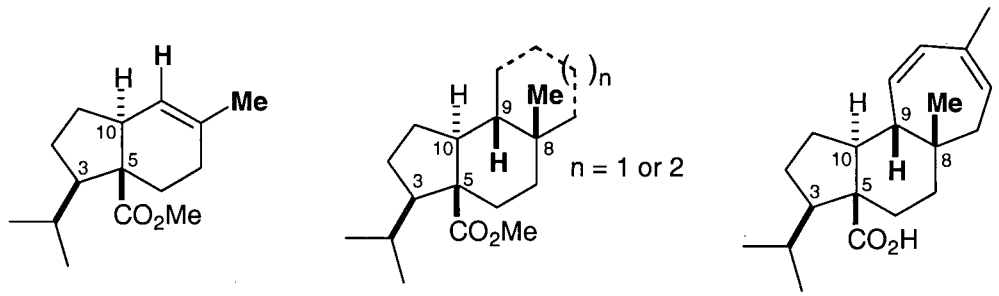
The fact that the relative stereochemistry at C-10 (mulinane numbering) could not be controlled, combined with the difficulties in obtaining alcohol **194** exclusively from the hydroboration of alkene **195** led us to abandon this synthetic approach. At this point it was apparent that the seven-membered annulation method developed by Piers *et al.*[34] would not yield access to (±)-isomulinic acid (**39**). However, the intriguing synthetic challenge posed by this natural product prompted the formulation of a new synthetic plan.

3.4.3 Second synthetic approach to (±)-isomulinic acid

3.4.3.1 Retrosynthetic analysis

The work described in section **3.4.2.2** made it clear that the presence of a carbonyl group adjacent to C-10 jeopardized the integrity of the carbon chirality center at that position. Therefore, the planned use of any intermediates in which the methine group at C-10 was activated, and thus prone to epimerization, was avoided.

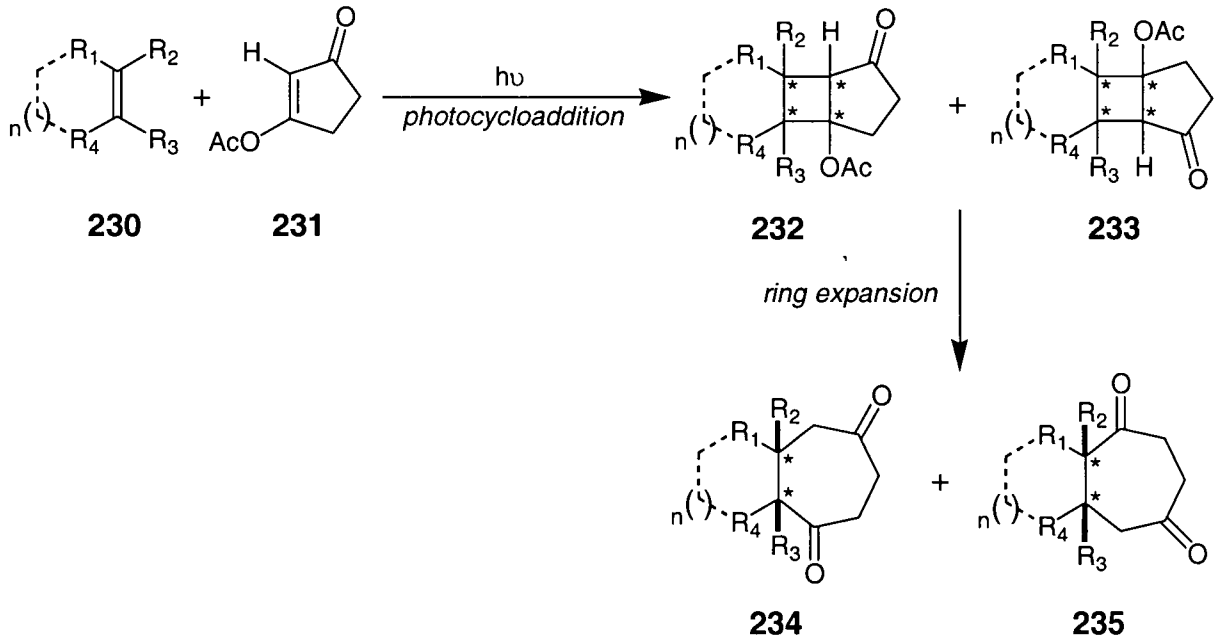
The second synthetic approach to the mulinane family of natural products focused on trying to quickly establish a tricyclic intermediate, exemplified by the general structure **229** (**Figure 3.16**), which could potentially be elaborated to the final product. Note that structure **229** has in place all the carbon chirality centers present in **157** with the correct relative configuration. Recall that compound **157** can, in principle, give rise to isomulinic acid (**39**, see **Scheme 3.2**). At this stage, the size and the functionalization of the third ring, which is to become the seven-membered ring in the final product, was left undefined. It was envisioned that the relative stereochemistry at C-8 and C-9 of **229** would be established during the photocycloaddition of alkene **228** to a suitable partner. Note that bicycle **228** has in place three of the five carbon chirality centers present in the proposed tricyclic structure (**229**). Note also the planned use of a methoxycarbonyl group at C-5 in **228** as a surrogate for the carboxylic acid moiety of **157**.



228 **229** **157**

Figure 3.15: Key proposed intermediates in the second retrosynthesis of (±)-isomulinic acid (39)

Two photochemical processes for the construction of carbocycles were considered. De Mayo and coworkers[122] have demonstrated that the photocycloaddition of an alkene (**230**) to a vinylogous anhydride such as **231** can be used to construct seven-membered rings. Note that the double bond of alkene **230** may be embedded within a ring. An overview of this useful reaction sequence is shown in **Scheme 3.26**. The photocycloaddition can, in theory, give rise to a total of eight possible products. These can be divided into two subsets of regioisomers, which are exemplified by **232** and **233**. Each subset may contain up to four isomers which arise from photocycloaddition at either face of alkene **230** and from the *endo* and *exo* modes of photocycloadditon. The number of isomers is reduced to four during the ring expansion step (**234**, **235** and their corresponding diastereomers arising from photocycloaddition on the other face of alkene **230**).



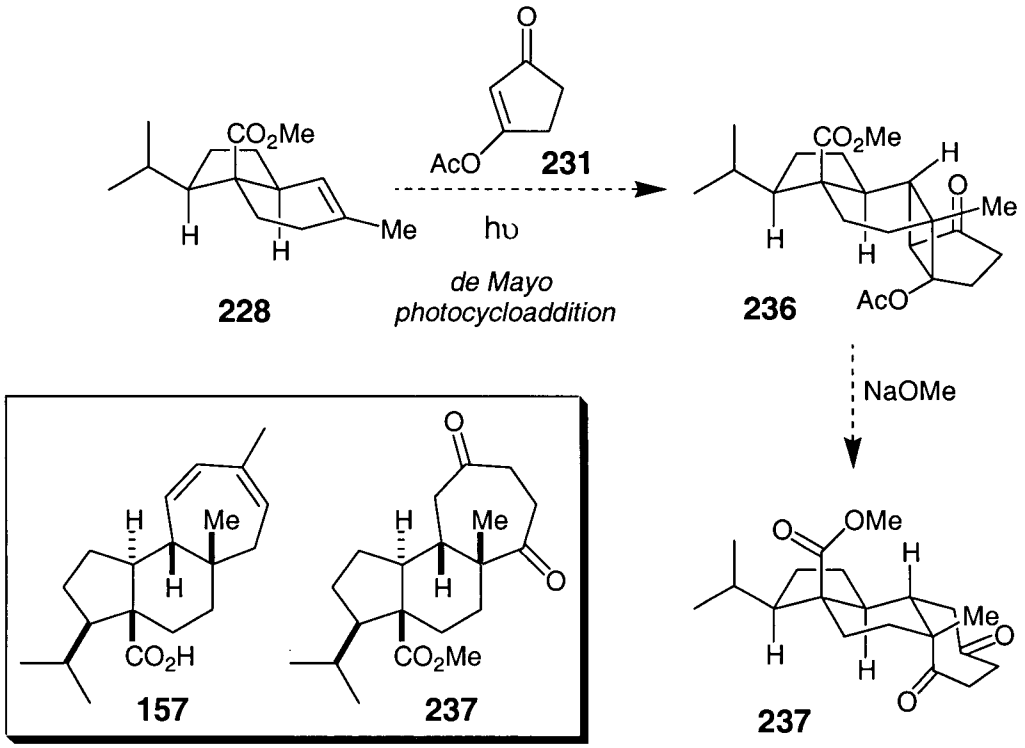
230 **231** **232** **233**

234 **235**

Scheme 3.26: Overview of the de Mayo reaction[112]

Analysis of molecular models of alkene **228** indicates that it should exist in the conformation depicted in **Scheme 3.27**, and that the β-face of the molecule is blocked by the methoxycarbonyl group. As a result, the vinylogous anhydride **231** should approach the double bond from the less sterically hindered α-face during the photocycloaddition. Therefore the major photocycloaddition product should be

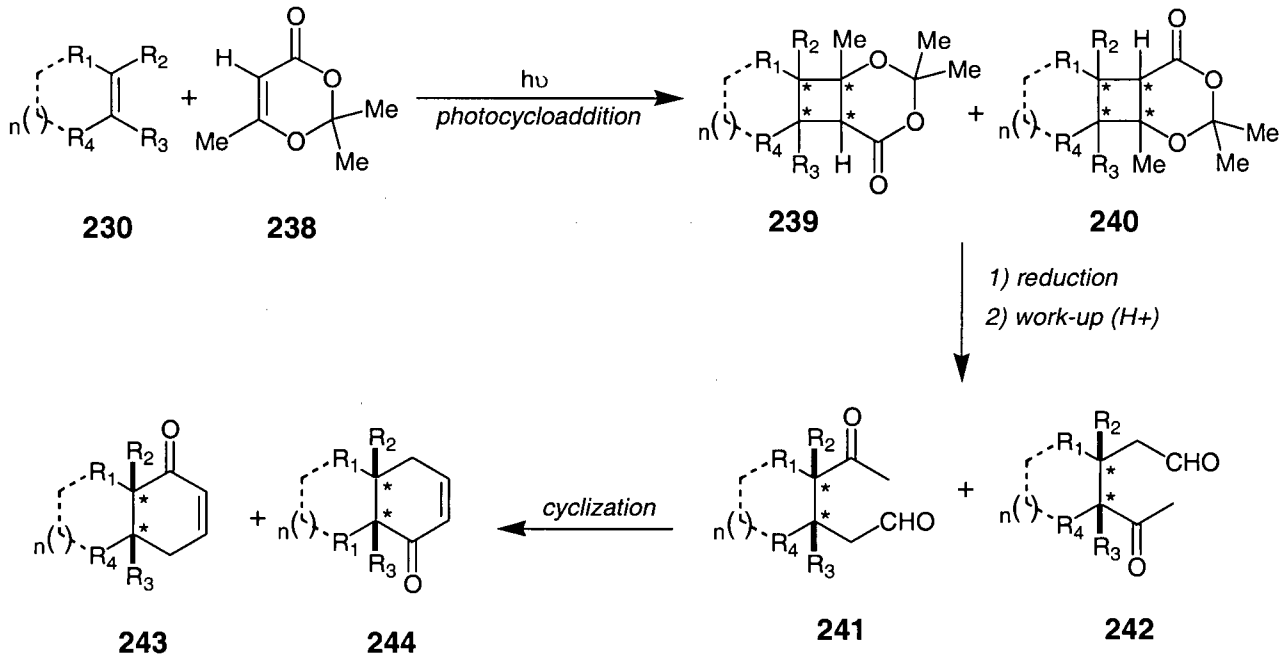
compound **236**. Treatment of compound **236** with NaOMe should promote the strain-driven ring expansion and furnish tricycle **237**. Note that **237** possesses all five carbon chirality centers present in **157** (**Figure 3.15**) with the correct relative configuration. At this stage no specific plan was drawn for the elaboration of diketone **237** to compound **157**. However, the functional groups on the seven-membered ring should allow for the preparation of the desired diene.



Scheme 3.27: Possible construction of 237 through a de Mayo reaction

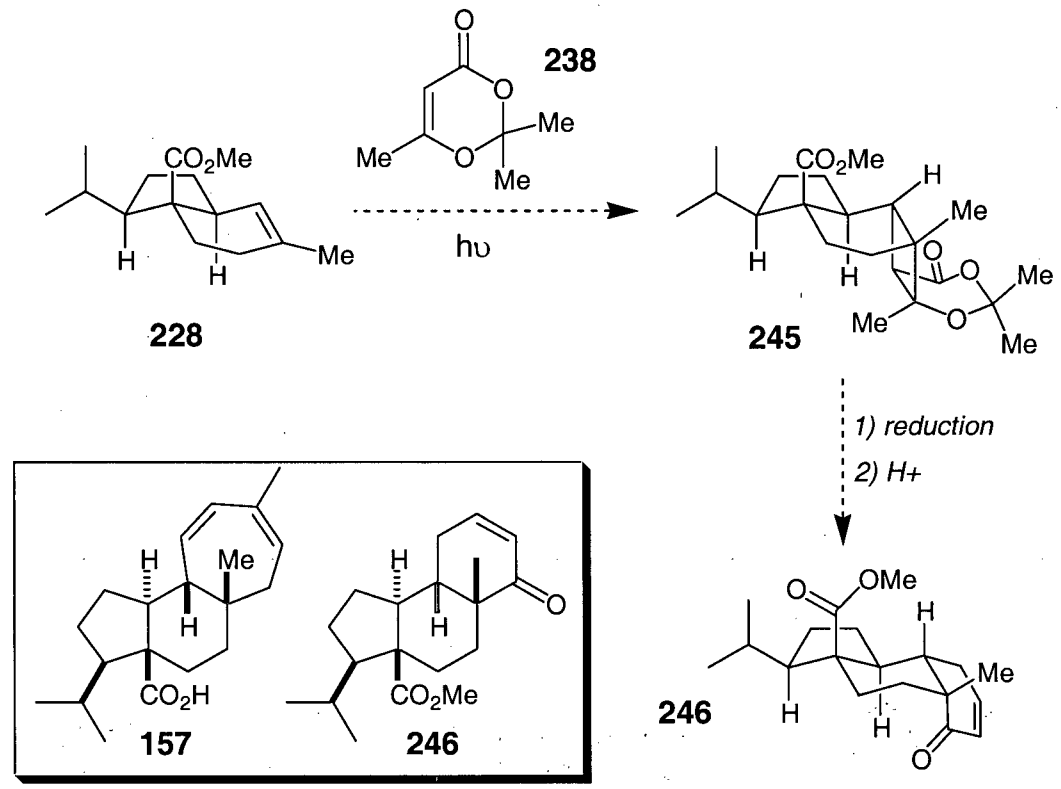
The second and lesser known photochemical process that could be potentially used for the preparation of a tricyclic structure such as **229** was developed by Baldwin and Wilkinson.[123] An overview of the reaction sequence is presented in **Scheme 3.28**. Photochemical cycloaddition of **230** to the vinylogous carbonate[124] **238** can yield up to eight possible products. As before, these can be subdivided into two subsets of regioisomers (**239** and **240**). Each subset may contain up to four isomers which arise from photochemical cycloaddition at either face of alkene **230** and from the *endo* and *exo* modes of photochemical cycloaddition. The number of isomers is reduced to four during the reduction of the ester carbonyl and the ensuing, strain-driven, carbon bond

cleavage (**241**, **242** and their corresponding diastereomers arising from photocycloaddition on the other face of alkene **230**). Keto aldehydes **241** and **242** readily undergo an aldol condensation to form enones **243** and **244**. An intramolecular version of this photocycloaddition reaction has been developed by Winkler[190] and has been employed in the total synthesis of challenging natural products.[191,192]



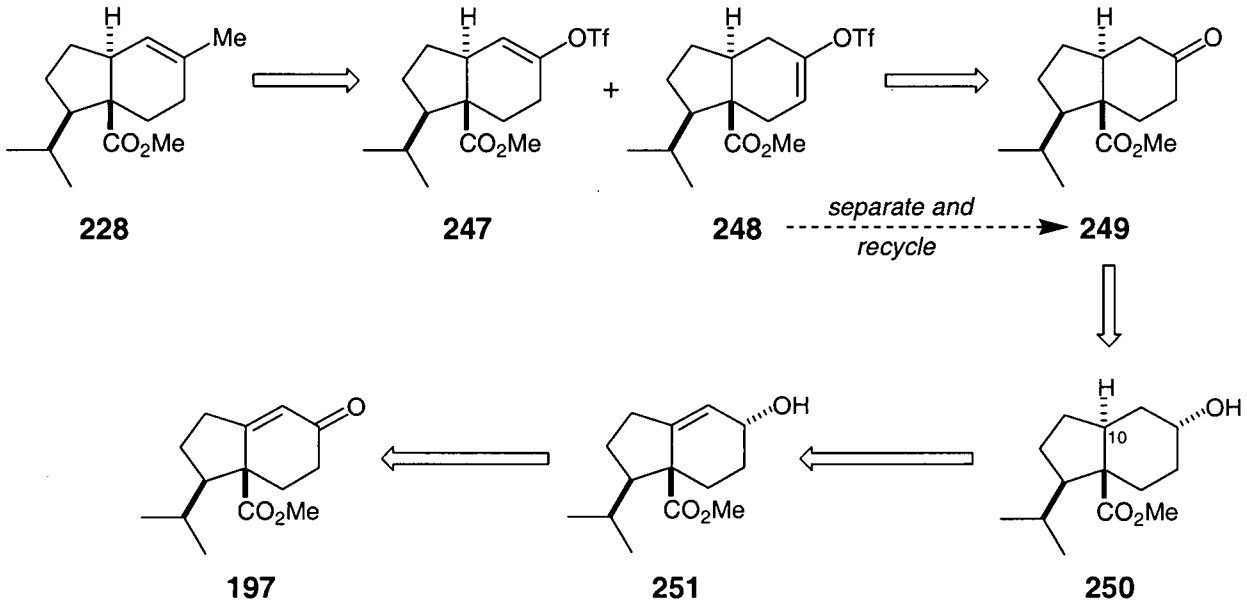
Scheme 3.28: Overview of the photocycloaddition-reduction-cyclization sequence developed by Baldwin[123]

Inspection of molecular models of alkene **228** and the vinylogous carbonate **238** indicates that their major photocycloaddition product should be **245** (**Scheme 3.29**). Treatment of **245** with DIBAL-H, followed by a suitable work-up procedure should furnish enone **246**. Note that **246** has in place the five carbon chirality centers present in **157** with the correct relative configuration. At this stage no specific plan was drawn for the elaboration of enone **246** to compound **157**. However, the functional groups on the six-membered ring should allow for the preparation of the desired diene.



Scheme 3.29: Possible construction of tricycle 246 using the reaction sequence developed by Baldwin.

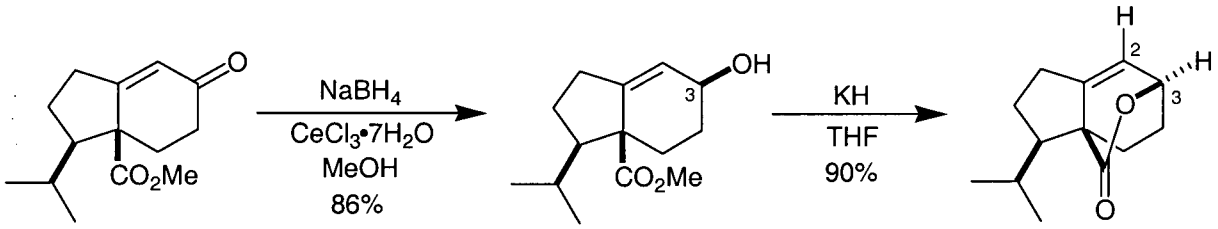
At this stage the synthetic problem is reduced to the preparation of alkene **228**. The initial strategy involved the preparation of **228** from enol triflate **247** and a methyl cuprate (**Scheme 3.30**). It was anticipated that a mixture of enol triflates **247** and **248** would be obtained from ketone **249**, therefore, a separation and recycle process was part of the plan. Ketone **249** was expected to be accessible from alcohol **250**. A directed homogeneous hydrogenation[106,107] of allylic alcohol **251** was expected to furnish alcohol **250**, which has the correct relative configuration at the newly formed carbon chirality center (C-10). It was anticipated that the hydroxyl group of alcohol **251** would exert a stronger directing effect than the methoxycarbonyl group.[125] The preparation of alcohol **251** from enone **197** was expected to be a straightforward process.



Scheme 3.30: Retrosynthetic analysis of alkene 228

3.4.3.2 Second synthetic approach to (±)-isomulinic acid

The reduction of enone **197** to alcohol **252** was easily accomplished under Luche conditions[126,127] (**Scheme 3.31**). A small amount (5%) of the C-3 epimer of alcohol **252** was also generated, but could be easily separated from the desired material using flash column chromatography on silica gel. The IR spectrum of **252** contained a strong absorption at 3383 cm^{-1}, which indicated the presence of the hydroxyl function. The carbinol proton was observed as a broad signal at $\delta = 4.22$ and the alkenyl proton was observed as a broad singlet at $\delta = 5.46$ in the ^1H NMR spectrum. An HRMS measurement of the parent ion was consistent with the molecular formula.

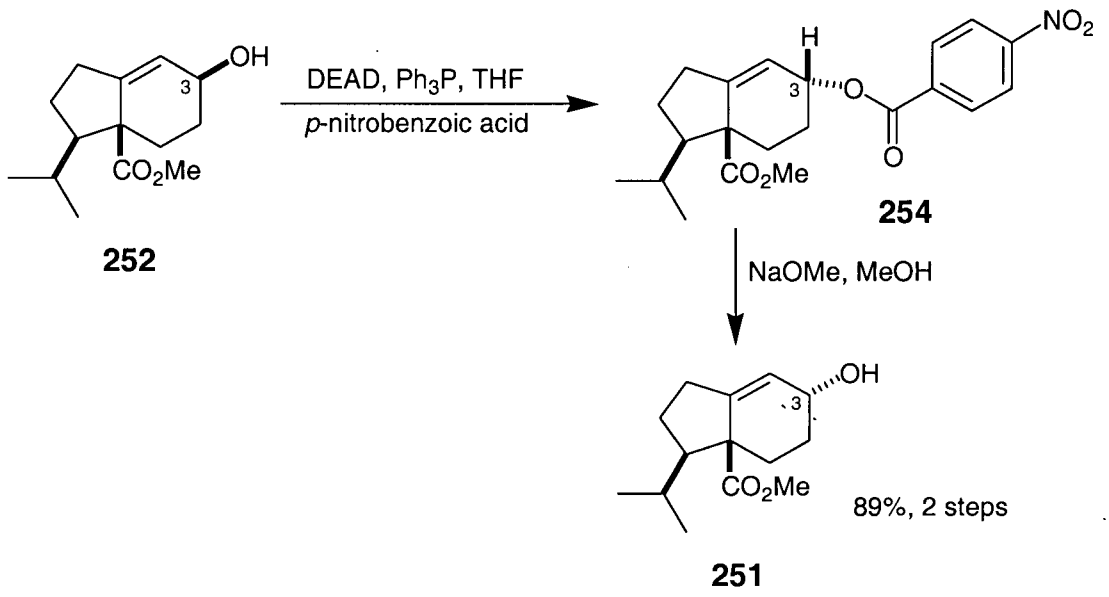


197 **252** **253**

Scheme 3.31: Preparation of alcohol 252 and lactone 253

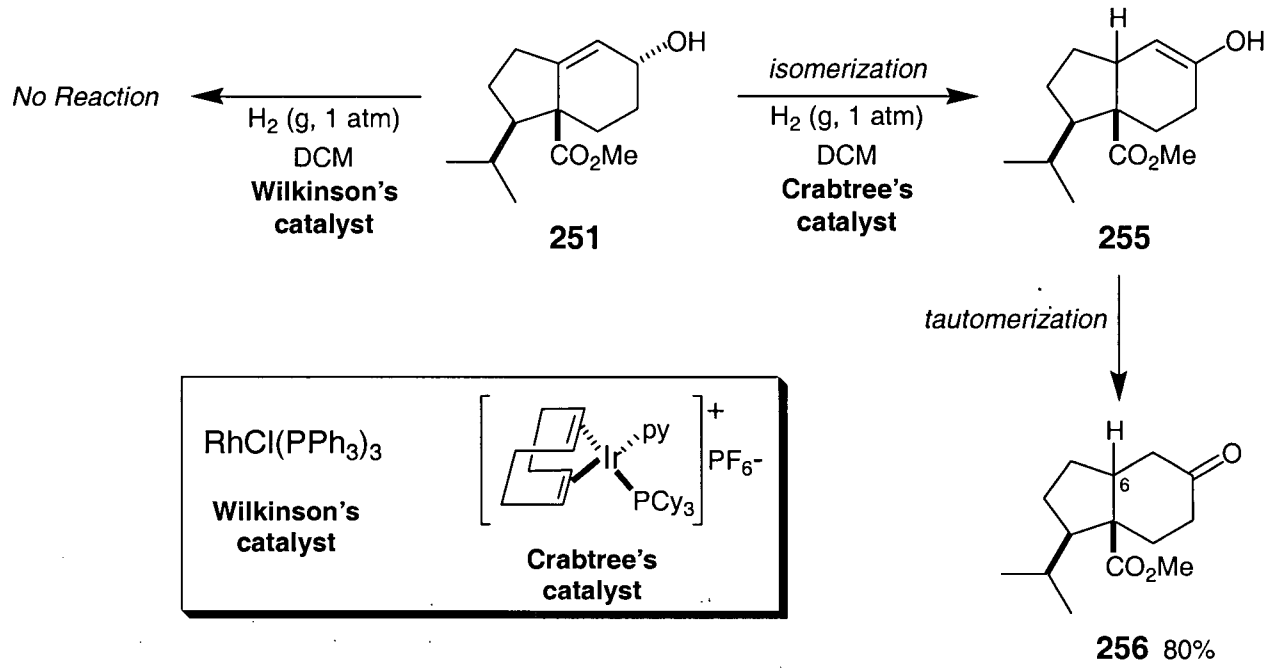
The relative configuration at C-3 was easily confirmed by formation of the corresponding bridged δ-lactone (**253**) when alcohol **252** was treated with a stoichiometric amount of KH. Lactone **253** exhibited a strong carbonyl stretching absorption at 1742 cm^{-1}. The ^1H NMR spectrum showed that the C-3 proton (observed as a ddd at $\delta = 5.03$-5.11) and the alkenyl proton at C-2 (observed as a ddd at $\delta = 6.06$-6.12) shared a mutual coupling constant of 5.0 Hz.

The configuration at C-3 of allylic alcohol **252** was inverted using the method developed by Mitsunobu[128] (**Scheme 3.32**). As expected, the IR spectrum of alcohol **251** showed an absorption at 3428 cm^{-1}, which accounted for the hydroxyl group, and a strong absorption at 1725 cm^{-1} due to the ester carbonyl function. The carbinol proton was observed as a broad signal at $\delta = 4.06$ in the ^1H NMR spectrum.



Scheme 3.32: Inversion of configuration at C-3 of allylic alcohol 252

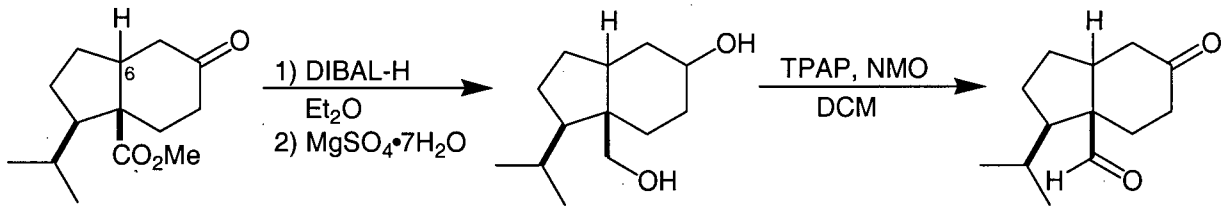
With alcohol **251** in hand, the stage was set for the crucial directed homogeneous hydrogenation[106,107] which would establish the carbon chirality center at C-10 (mulinane numbering). No reaction was observed when Wilkinson's catalyst[66] was used in an attempted hydrogenation (**Scheme 3.33**). Treatment of alcohol **251** with a catalytic amount of Crabtree's catalyst[65,129,130] under hydrogen at one atmosphere provided a mixture of products (**Scheme 3.33**). GC-LRMS analysis of the mixture indicated that the major component had the same molecular mass as the starting material. In addition, TLC analysis of the mixture showed that the major product was much less polar than alcohol **251**. These observations suggested that allylic alcohol **251** had isomerized to enol **255**, which tautomerized to the corresponding ketone (**256**).



Scheme 3.33: Attempted homogeneous hydrogenation of alcohol 251 using Wilkinson's catalyst and Crabtree's catalyst

Ketone **256** exhibited a carbonyl absorption at 1724 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum did not show evidence of a carbinol proton. A resonance at $\delta =$ 212.6 in the ^{13}C NMR spectrum was attributed to the ketone carbonyl carbon. Although the structure of ketone **256** could be fully assigned, it was not possible to determine the relative configuration of the newly formed carbon chirality center by spectroscopic means.

The relative configuration at C-6 of ketone **256** was determined indirectly. Keto ester **256** was efficiently reduced to diol **257** with DIBAL-H. This material was oxidized to the corresponding keto aldehyde (**258**) using Ley's method[88] (**Scheme 3.34**). Keto aldehyde **258** exhibited carbonyl stretching absorptions at 1721 cm^{-1} and 1709 cm^{-1} in the IR spectrum. The ^{13}C NMR spectrum displayed two carbonyl resonances at $\delta =$ 203.5 and $\delta =$ 212.0, which were attributed to the aldehyde and ketone carbonyl carbons respectively. A singlet at $\delta =$ 9.71 in the ^{1}H NMR spectrum provided further evidence for the aldehyde moiety.

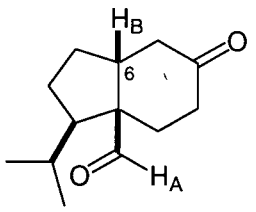


256 **257** **258**

73%, 2 steps

Scheme 3.34: Preparation of keto aldehyde 258

A full suite of NMR experiments allowed the complete structural assignment of keto aldehyde **258**. The relative configuration at C-6 was determined using a selective 1D NOE difference experiment (**Figure 3.15**). Enhancement of the angular proton (H_B) upon irradiation of the aldehyde proton (H_A) provided strong evidence for the *cis*-fusion of keto aldehyde **258**.



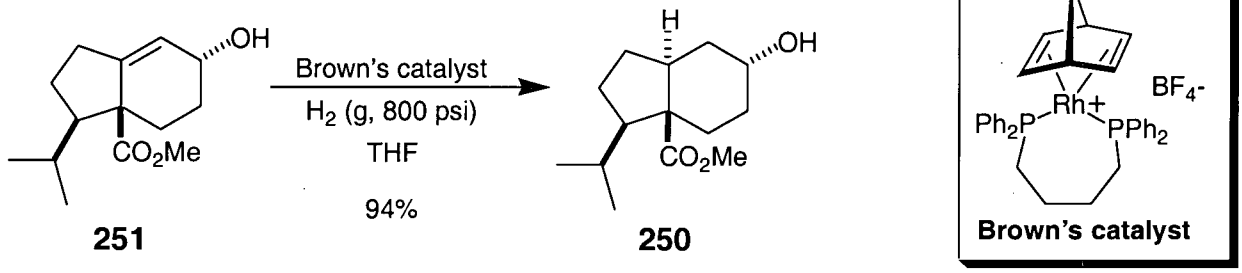
H_A: δ = 9.71 (s)

H_B: δ = 2.60-2.71 (dddd, J = 10.4, 6.8, 6.4, 5.9 Hz)

irradiation of H_A enhances H_B

Figure 3.15: Selected NOE difference data for keto aldehyde 258

In view of these results, it became necessary to explore other methods for directed hydrogenation. Evans[131] has demonstrated that Brown's catalyst[132] can be used to effect directed hydrogenations of allylic alcohols similar to **251**. This process is rather sensitive to substrate concentration, hydrogen concentration and catalyst load. After some experimentation, the desired *trans*-fused alcohol (**250**) could be obtained as the sole product from the directed hydrogenation of **251**.

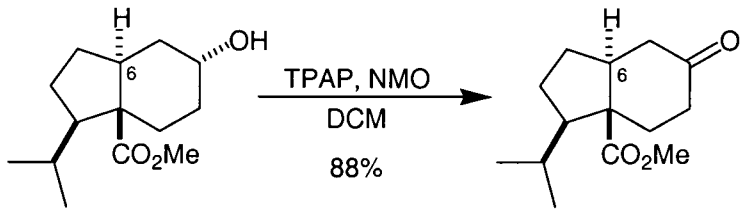


251 **250**

Scheme 3.35: Directed homogeneous hydrogenation of allylic alcohol 251 using Brown's catalyst

The carbinol proton of alcohol **250** was observed as a multiplet at $\delta = 4.02\text{-}4.10$ in the ^{1}H NMR spectrum. The previously observed alkenyl proton signal was notably absent. A *J*-mod ^{13}C NMR experiment demonstrated the presence of five methylene groups and a total of seven methyl and methine groups. An HRMS measurement of the parent ion was consistent with the molecular formula of alcohol **250**.

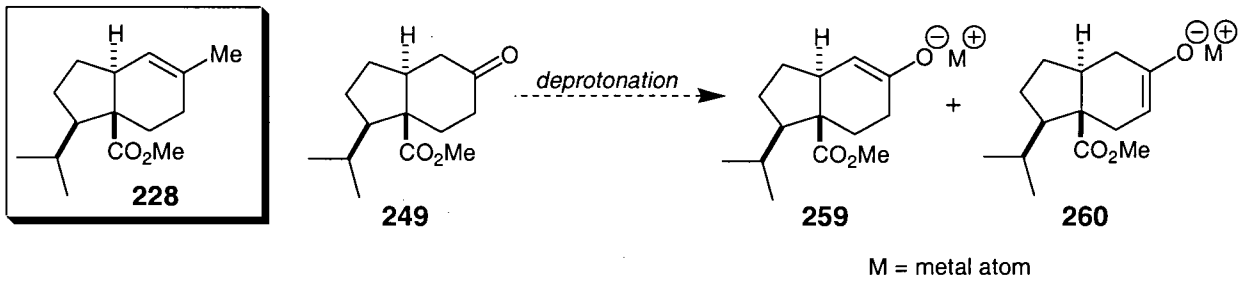
Alcohol **250** was cleanly oxidized to the corresponding ketone using Ley's method[88] (**Scheme 3.36**). A resonance at $\delta = 210.9$ in the ^{13}C NMR spectrum of ketone **249** was attributed to the ketone carbonyl carbon. The molecular formula of **249** was confirmed by an HRMS measurement of the parent ion. A fortuitous dispersion of signals in the ^{1}H NMR spectrum allowed the complete structural assignment of ketone **249**. The relative configuration of the carbon chirality center at C-6 could not be verified by spectroscopic means, but was assigned to be as depicted in **Scheme 3.36** by comparison to ketone **256**.



250 **249**

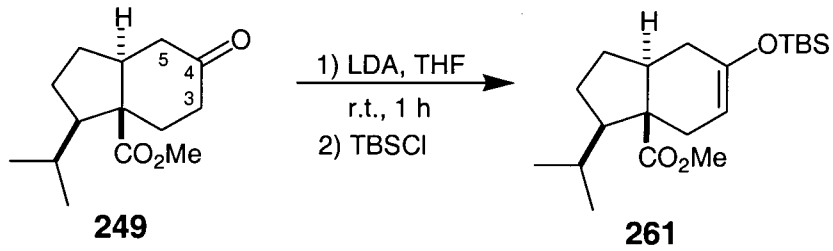
Scheme 3.36: Preparation of ketone 249

The synthetic plan called for the preparation of alkene **228** through the intermediacy of the related enolate (**259**, see **Scheme 3.37**). As mentioned previously, it was expected that a mixture of enolates (**259** and **260**) would be obtained upon deprotonation of ketone **249** with strong base.

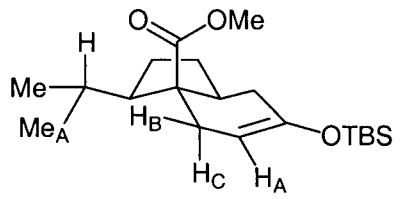


Scheme 3.37: Planned deprotonation of ketone 249

Treatment of ketone **249** with strong base under conditions which allow the formation of the most thermodynamically stable product (e.g. a slight deficiency of base with respect to the amount of ketone used), followed by trapping of the enolate with a sililating agent provided a single enol ether (**261**) as the major product (**Scheme 3.38**). The position of the double bond was established using a series of selective 1D NOE difference experiments as shown in **Figure 3.18**.



Scheme 3.38: Formation of enol ether 261



261

H_A; δ = 4.80-4.89 (m)

H_B; δ = 2.88-2.98 (dd, J = 16.2, 6.4 Hz)

H_C; δ = 1.80-1.91 (m)

Me_A; δ = 0.96 (d, J = 6.4 Hz)

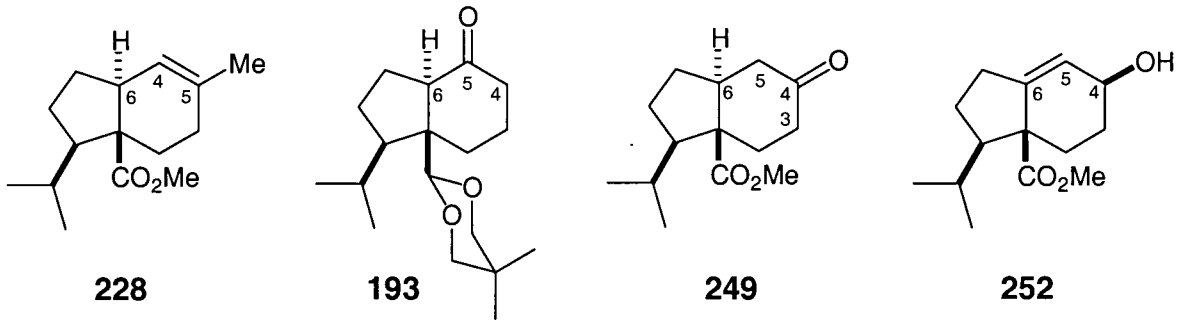
irradiation of H_A enhances H_B and H_C

irradiation of H_B enhances H_A, H_C and Me_A

Figure 3.18: Selected NOE difference data for enol ether 261

Note that the C-5 methylene group of ketone **249** (see **Scheme 3.38**) is sterically hindered relative to the methylene group at C-3 by virtue of the adjacent five-membered ring. Consequently, it was expected that the deprotonation of ketone **249** under kinetic conditions, followed by trapping of the enolate with a silylating agent would favour the formation of enol ether **261**. Therefore it appeared that a feasible preparation of alkene **228** would not be achieved using the synthetic plan outlined in **Scheme 3.30**.

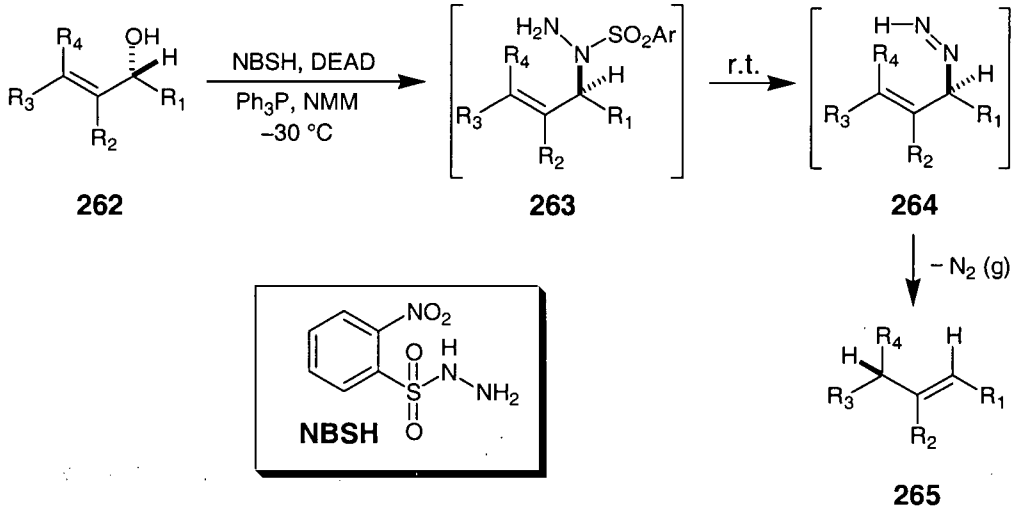
It is clear that the preparation of alkene **228** from enone **197** (**Scheme 3.31**) required the installation of the carbon chirality center at C-6 with the correct relative configuration, and the selective activation of C-4 and C-5 (**Figure 3.19**). The work outlined in section **3.4.2.2** suggested that a substrate similar to ketone **193**, in which C-4 and C-5 are activated by the carbonyl group, would not be a suitable intermediate in a synthesis of alkene **228**. Moreover, it has been established that although the carbonyl group at C-4 of ketone **249** activated C-5 and did not jeopardize the integrity of the carbon chirality center at C-6, this substrate was not useful in the preparation of alkene **228**. After some thought, it became apparent that the allylic alcohol moiety embedded in compound **252** activated the desired carbon atoms. It seemed that it should be possible to use this feature of alcohol to **252** to prepare alkene **228**.



228 193 249 252

Figure 3.19: Structures of alkene 228, ketones 193 and 249, and alcohol 252

At this time two literature reports inspired a second possible strategy for the preparation of alkene **228**. The first of these was Myers' highly regio- and stereoselective method for the reductive 1,3-transposition of allylic alcohols[133-135] (**Scheme 3.39**). Treatment of an allylic alcohol (**262**) with NBSH[136,137] under Mitsunobu[128] conditions at –30 °C results in the formation of the corresponding *N*-allylic sulfonyl-hydrazine (**263**). This material decomposes at higher temperatures to form an allylic diazene intermediate (**264**). Diazene **264** undergoes elimination of molecular nitrogen which results in the reductive transposition of the double bond to form alkene **265**.

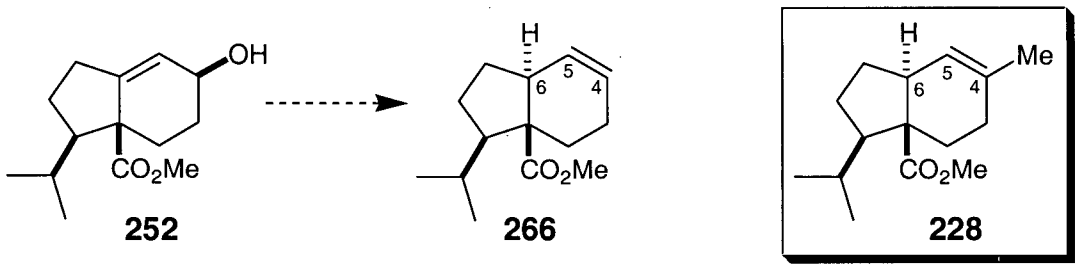


262 263 264 265

Scheme 3.39: Myers' method for reductive 1,3-transposition of allylic alcohols[34]

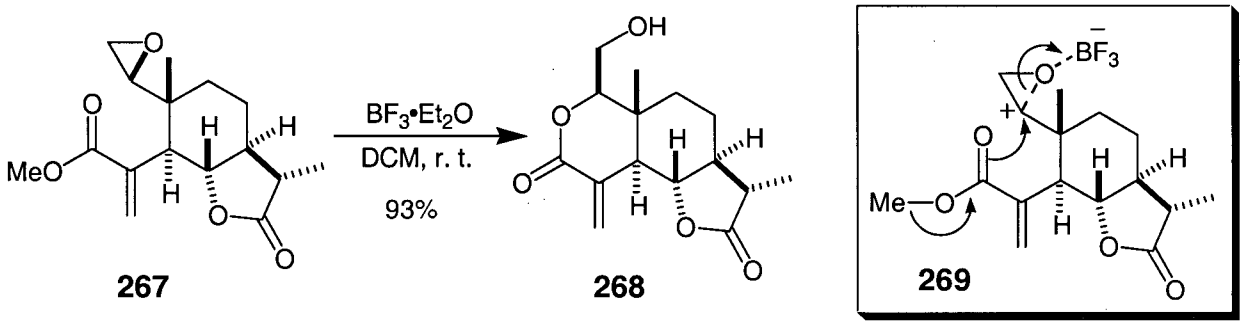
It appeared likely that this method could be utilized to prepare alkene **266** from allylic alcohol **252** (**Scheme 3.40**). Note that alkene **266** possesses the correct relative

configuration at C-6 and has C-4 and C-5 activated by virtue of the double bond. In order to prepare alkene **228** it was necessary to install a carbon atom on C-4, and this would require the discrimination between C-4 and C-5.



Scheme 3.40: Planned preparation of alkene 266 from allylic alcohol 252

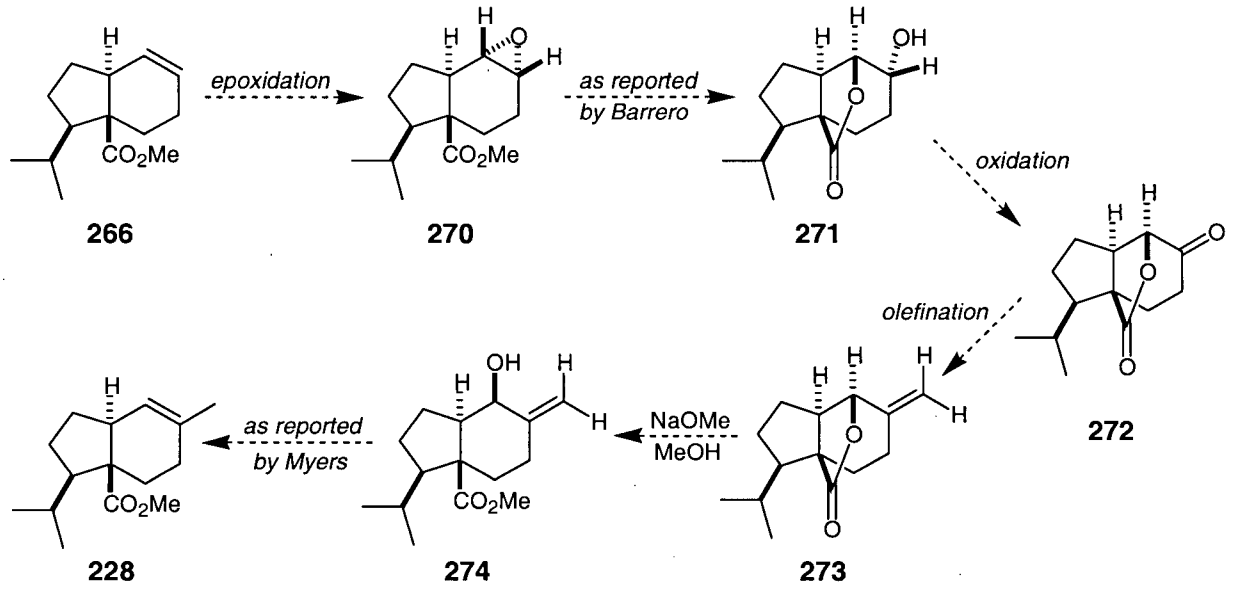
Barrero *et al.*[138] have shown that substrates with appropriately positioned epoxide and methoxycarbonyl groups, such as **267**, can be efficiently converted to hydroxylactones (**268**) upon treatment with a Lewis acid (**Scheme 3.41**). The reaction is thought to occur in a concerted fashion as shown in **269**.



Scheme 3.41: Formation of hydroxylactone 268 from epoxyester 267 as demonstrated by Barrero *et al.*[138]

In the context of a planned synthesis of alkene **228**, alkene **266** would have to be oxidized to oxirane **270** (**Scheme 3.42**). For steric reasons, the relative configuration of the carbon chirality centers at C-4 and C-5 of epoxide **270** was expected to be as shown. Treatment of **270** with a Lewis acid should furnish the expected bridged hydroxylactone (**271**). Alcohol **271** should be readily oxidized to

ketone **272**, which should furnish alkene **273** upon selective olefination. It was hoped that lactone **273** would provide allylic alcohol **274** upon treatment with NaOMe in MeOH. In principle, Myers' method for reductive transposition of allylic alcohols[133] would allow access to alkene **228** from alcohol **274**.

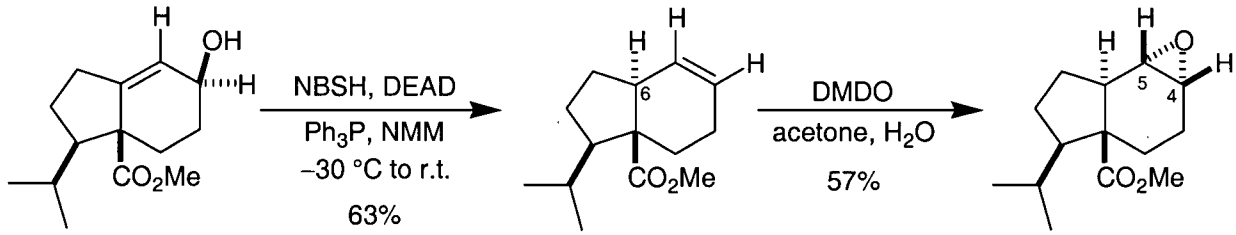


Scheme 3.42: Implementation of Barrero's[138] and Myers'[134] methods in a planned synthesis of alkene 225

Subjection of alcohol **252** to Myers' conditions for reductive transposition of the double bond furnished the desired alkene, albeit in modest yield (**Scheme 3.43**). The alkene function of **266** was evidenced by two signals at δ = 5.40-5.49 and δ = 5.68-5.75 with a mutual coupling constant of 9.9 Hz in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum displayed two resonances at δ = 126.6 and δ = 129.4 which provided further evidence for the presence of the double bond. No indication of a hydroxyl group was found in the IR spectrum. Finally, an HRMS measurement of the parent ion was consistent with the molecular formula of the requisite alkene. No effort to establish the relative configuration of the carbon chirality center at C-6 of alkene **266** was made at this stage. However, based on the mechanism for the reductive transposition of the double bond, the configuration at C-6 was assumed to be as shown in **Scheme 3.43**.

The next step involved the diastereoselective epoxidation of alkene **266** to epoxide **270**. Analysis of molecular models of alkene **266** indicates that it should adopt a conformation in which the β-face of the double bond is blocked by the methoxycarbonyl group. As a result, the oxidizing agent should approach the double bond from the less sterically hindered α-face. Therefore, the relative configuration at C-4 and C-5 of epoxide **270** was anticipated to be as depicted in **Scheme 3.43**.

The epoxidation of alkene **266** was accomplished smoothly under the action of dimethyl dioxirane (DMDO). The ^{1}H NMR spectrum of a crude mixture of products indicated that two epoxides had been obtained in approximately 10:1 ratio. Fortunately, the major product could be isolated using flash column chromatography on silica gel. The ^{1}H NMR spectrum and the ^{13}C NMR spectrum of epoxide **270** both showed the correct number of signals. The absence of any signals in the olefinic region of the ^{1}H NMR spectrum of **270**, and the appearance of two signals at δ = 2.97-3.02 and δ = 3.16-3.20 with a mutual coupling constant of 4.1 Hz clearly showed that the alkene moiety had been oxidized to the desired epoxide. Finally, the molecular formula of **270** was confirmed by an HRMS measurement of its parent ion. At this stage no efforts were made to establish the relative configuration at C-4 and C-5 of compound **270**.

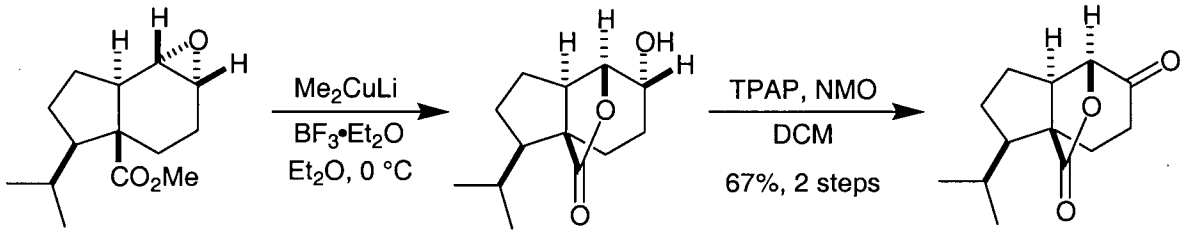


252 **266** **270**

Scheme 3.43: Preparation of epoxide 270

With access to sufficient amounts of epoxide **270**, the stage was set for the proposed lactonization-epoxide opening reaction under the conditions reported by Barrero *et al.*[138] Curiously, treatment of epoxide **270** with BF_3•Et_2O in DCM at 0 °C resulted in the formation of a complex mixture of products. However, treatment of epoxide **270** with BF_3•Et_2O in the presence of lithium dimethyl cuprate in Et_2O at 0 °C

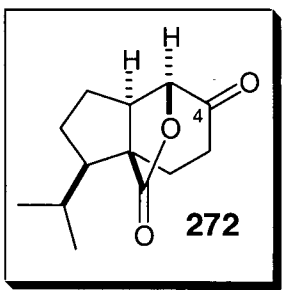
led to the formation of hydroxylactone **271** (**Scheme 3.44**). This material did not lend itself to chromatographic purification on silica gel and was, therefore, directly oxidized to the corresponding keto lactone (**272**). Two absorptions at 1798 cm^{-1} and at 1742 cm^{-1} in the IR spectrum of **272** clearly indicated the presence of a γ-lactone and a ketone moiety, respectively. The molecular formula of **272** was confirmed by an HRMS measurement of its parent ion. The ketone carbonyl carbon was observed at δ = 204.5 and the lactone carbonyl was observed at δ = 177.1 in the ^{13}C NMR spectrum.

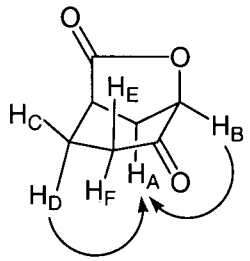


270 **271** **272**

Scheme 3.44: Preparation of keto lactone 272

Gratifyingly, the disperse nature of the ^1H NMR spectrum of keto lactone **272** facilitated the complete assignment of all the protons on the six-membered ring with the aid of a COSY experiment (**Figure 3.20**). This allowed the corroboration of the relative configuration of the carbon chirality center at C-6 through the use of two selective NOE difference experiments. It is interesting to note that the lack of coupling between H_A and H_B, and between H_C and H_F, indicates that the six-membered ring of **272** resides in a twist-boat conformation.





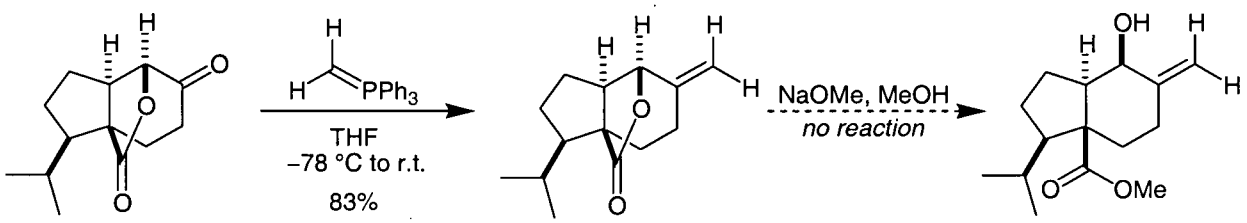
partial structure of **272**

H_A: δ = 2.32-2.38 (dd, J = 9, 9 Hz)
H_B: δ = 4.35 (s)
H_C: δ = 2.47-2.55 (dd, J = 12.7, 9.1 Hz)
H_D: δ = 1.66-1.76 (ddd, J = 12.7,11.5, 6.9 Hz)
H_E: δ = 2.59-2.69 (ddd, J = 16.5, 11.5, 9.1 Hz)
H_F: δ = 2.36-2.45 (dd, J = 16.5, 6.9, Hz)

irradiation of H_D and H_B both enhance H_A

Figure 3.20: Selected NMR data for keto lactone 272

At this stage it was necessary to install the carbon atom on C-4 of keto lactone **272**. Subjection of **272** to Takai[82-84,87] olefination conditions did not prove fruitful. The desired transformation was smoothly accomplished with the use of a Wittig phosphorane reagent (**Scheme 3.45**). The two exocyclic methylene protons of alkene **273** appeared as singlets at $\delta = 4.86$ and $\delta = 4.79$, and the carbinol proton appeared as a singlet at $\delta = 4.69$ in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum exhibited a carbonyl resonance at $\delta = 178.6$, two alkenyl resonances at $\delta = 144.5$ and $\delta = 108.7$, and a carbinol resonance at $\delta = 83.7$. The absorption at 1770 cm^{-1} in the IR spectrum of **273** was attributed to the γ-lactone carbonyl group. An HRMS measurement of the parent ion confirmed the molecular formula for **273**.



272 **273** **274**

Scheme 3.45: Attempted preparation of allylic alcohol 274

With the structure of **273** firmly established, the stage was set for the proposed methanolysis of the lactone moiety under basic conditions. Compound **273** turned out to be remarkably stable under these conditions. This result was rather surprising since it was expected that the strain in the six-membered ring of alkene **273** would be similar to that of keto lactone **272** (see **Figure 3.18**), and would therefore drive the methanolysis of the lactone moiety.

The failure to convert compound **273** to allylic alcohol **274** led us to abandon the approach to alkene **228** outlined in **Scheme 3.40** and **Scheme 3.42**. At this stage, a different and apparently more expedient approach to the mulinane diterpenoids was devised.

3.4.4 Third synthetic approach to (±)-isomulinic acid

3.4.4.1 Retrosynthetic analysis

The third synthetic approach to the mulinane diterpenoids was influenced by the results described in section **2.4.3.2** and by two reports in the literature which suggested a new and expedient strategy to establish the carbon chirality centers at C-8, C-9 and C-10 of the mulinane skeleton.

It has been shown that although ketone **249** can be prepared efficiently, enolate **259** could not be formed selectively (**Figure 3.19**). It appeared likely that if a carbon substituent was present at C-9 (as in **275**); it would be possible to selectively form an enolate such as **276** under thermodynamic conditions.

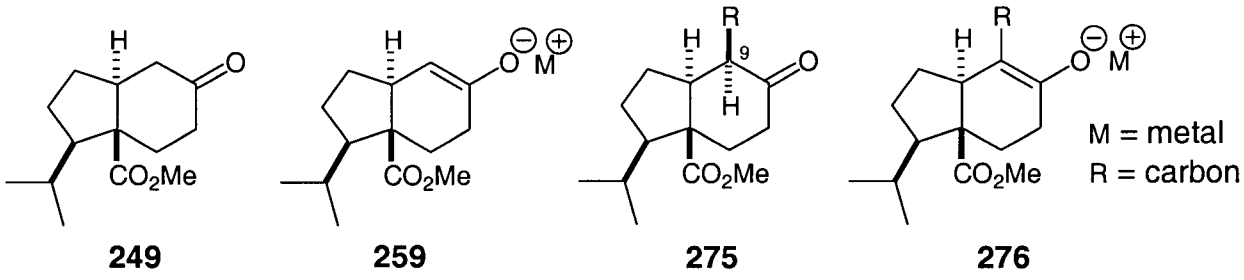


Figure 3.21: Structure of ketones 249 and 275 and of enolates 259 and 276

It was expected that a ketone such as **275** would be accessible through a directed hydrogenation of alcohol **277** (see **Figure 3.22**), followed by oxidation of the product. Alcohol **277**, in turn, would be prepared from enone **278** as before (see **Schemes 3.31** and **3.32**). It was realized that this idea would not prove useful in preparing alkene **228** as outlined in **Scheme 3.30** since the substituent at C-9 of **228** is a hydrogen atom. However, note that the carbonyl group of **275** activates C-9 and should allow for the inversion of configuration at that carbon to yield a system such as **279**, in which the substituent at C-9 is equatorial. Bicycle **279** possesses four of the five carbon chirality centers found in all the mulinane natural products (see **157**) with the correct relative configuration.

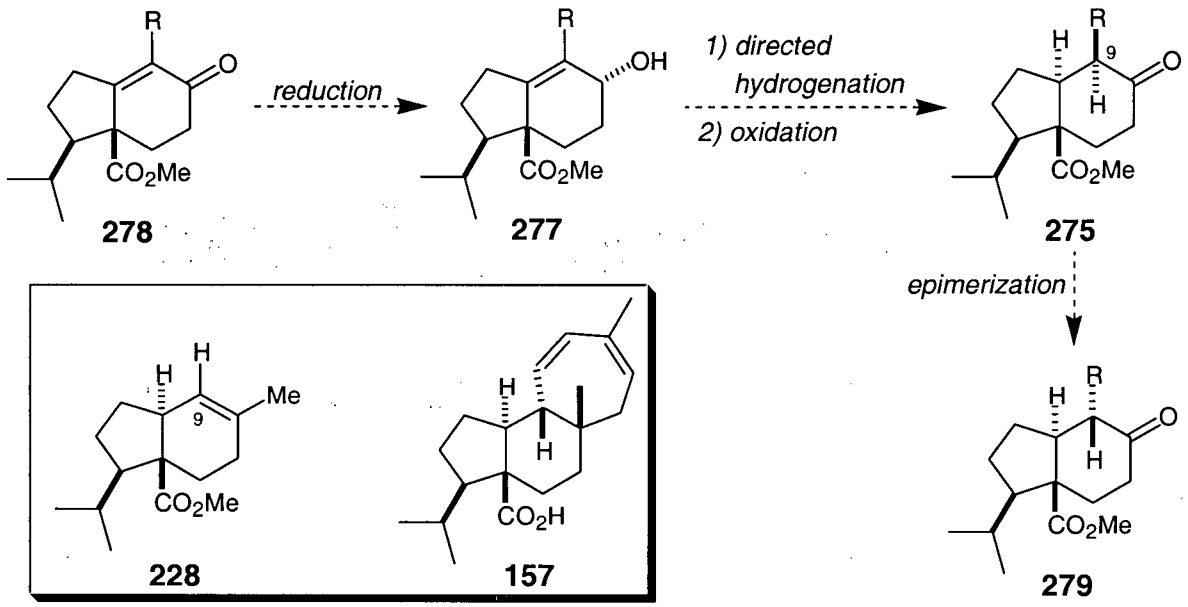
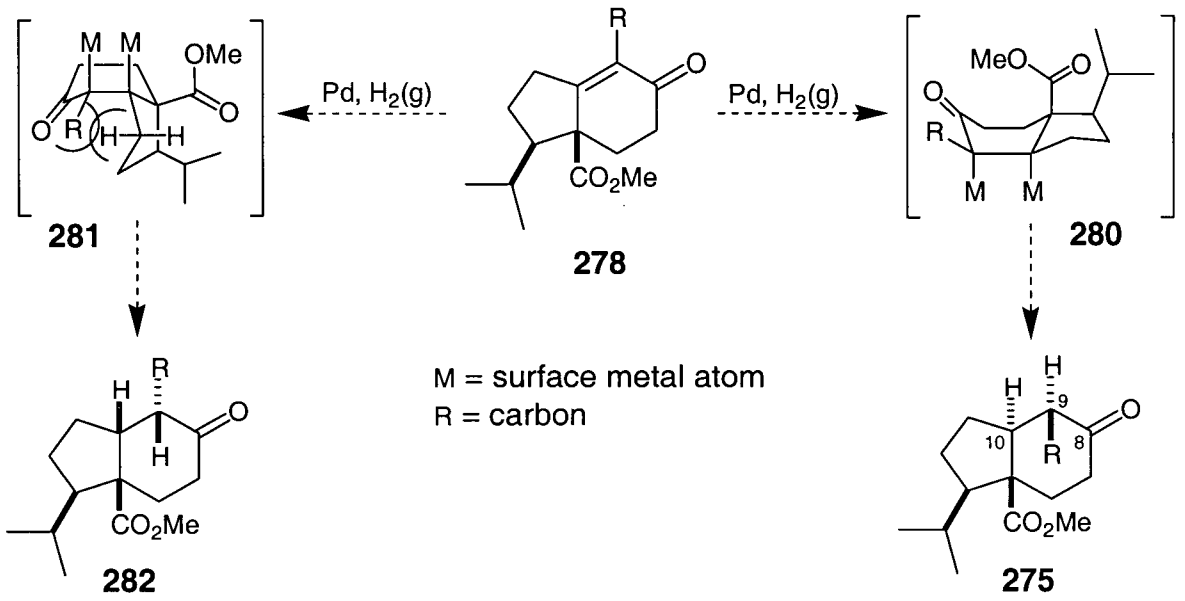


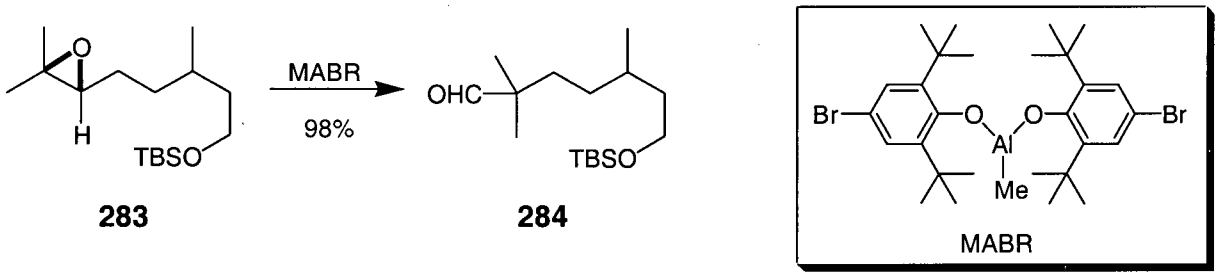
Figure 3.22: Potential preparation of ketone 279 from enone 278

A report from the literature indicated that hydrogenation of an enone such as **278** under heterogeneous conditions would likely yield the corresponding *trans*-fused system (**279**) after equilibration at C-9 of ketone **275** (**Scheme 3.46**). According to the classical Horiuti-Polanyi mechanism for hydrogenation of olefins over metal catalysts, the two hydrogen atoms add to the same side of the double bond. McKenzie[139] has pointed out that there is a stereoelectronic requirement for the two metal-carbon bonds in intermediates **280** and **281** to be eclipsed, which forces the six-membered ring into a boat conformation. Note that in intermediate **281**, which leads to the *cis*-fused product (**282**), the boat forces the R group to clash with one of the methylene protons on the five-membered ring. If the R group is sufficiently large, this non-bonded interaction will destabilize the complex. As a result, intermediate **280**, in which the boat forces the R group away from the five-membered ring, is favoured. The fact that a correlation exists between the size of the side chain (R) and the amount of *trans*-fused product observed in the heterogeneous hydrogenation of substrates similar to enone **278** supports McKenzie's proposal.



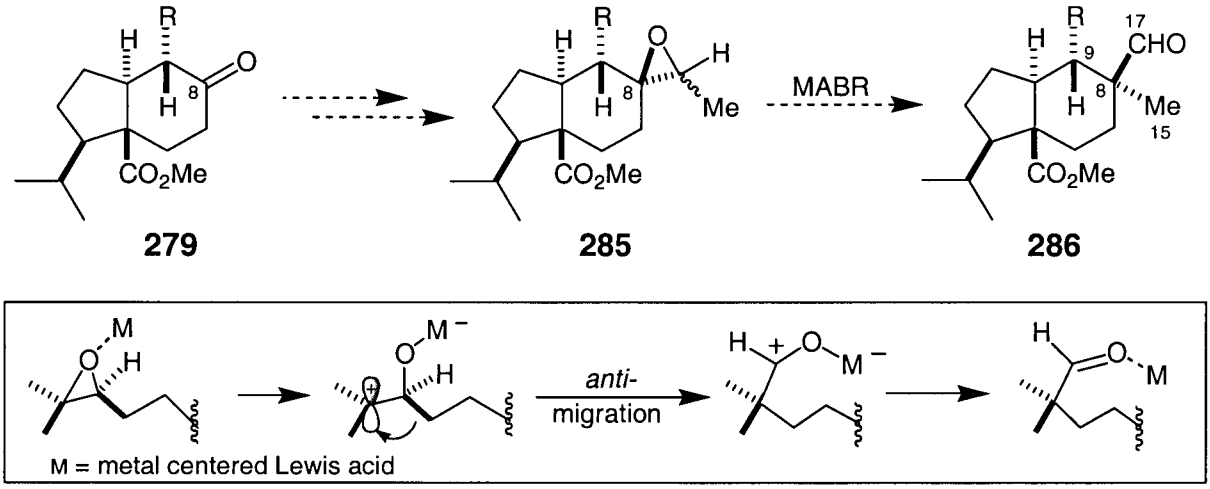
Scheme 3.46: Application of McKenzie's[139] rationale for the heterogeneous hydrogenation of enones in a proposed synthesis of ketone 275

If the hydrogenation depicted above proved successful in establishing the correct relative configuration at C-9 and C-10, it would still be necessary to establish the quaternary center at C-8. The efficient and stereoselective Lewis acid-catalyzed rearrangement of epoxides to tertiary aldehydes has been demonstrated by Yamamoto and coworkers[140] among others.[141] The example depicted in **Scheme 3.47** was particularly interesting since it indicated that this protocol might prove useful in establishing the carbon chirality center at C-8. Treatment of epoxide **283** with a stoichiometric amount of a bulky Lewis acid results in the formation of a tertiary aldehyde (**284**) in excellent yield.



Scheme 3.47: Preparation of a tertiary (284) aldehyde from a trisubstituted epoxide (283) as demonstrated by Yamamoto and coworkers.[140]

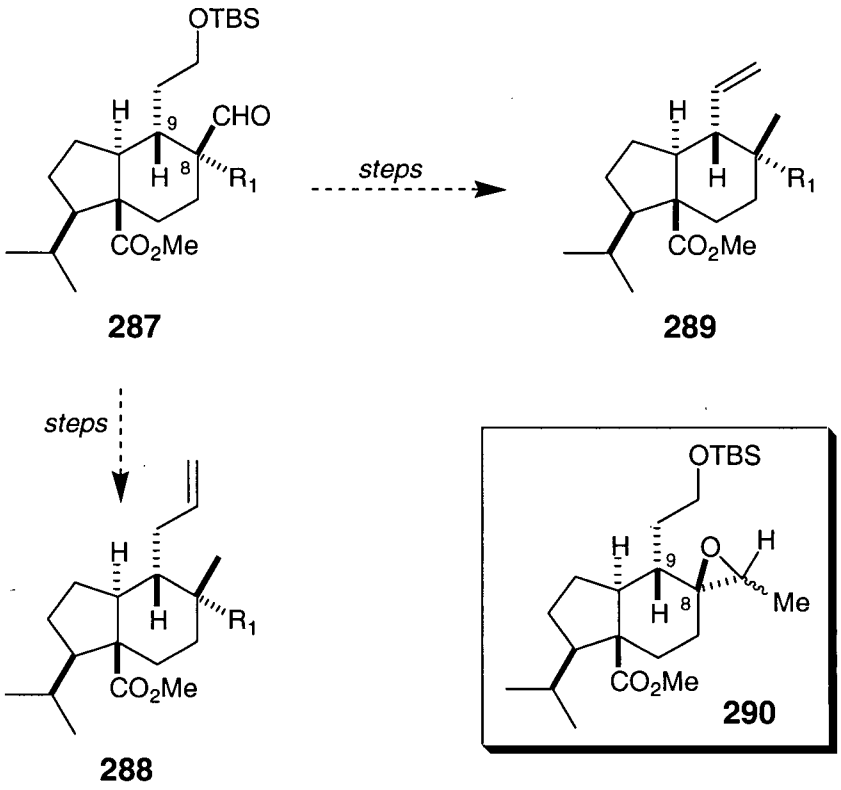
It seemed likely that an epoxide such as **285** could be readily synthesized from ketone **279** using standard methods (**Scheme 3.48**). The relative configuration at C-8 of **285** was expected to be as shown based on steric arguments. The relative configuration at the other epoxide carbon (which corresponds to C-17 in the natural product) does not need to be defined at any stage. It has been established that, during the epoxide rearrangement, the migration of the alkyl group occurs *anti* to the oxygen atom (see inset, **Scheme 3.48**). Therefore, it was expected that if an aldehyde was obtained from the rearrangement of **285**, the configuration at C-8 would be retained (as in **286**).



Scheme 3.48: Application of Yamamoto's epoxide rearrangement[140] to the planned preparation of aldehyde 286

It was expected that if the proposed rearrangement of epoxide **285** to aldehyde **286** proved successful, this approach could be extended to the construction of the mulinane carbocyclic skeleton. At this stage, no specific plan had been devised for the construction of the seven-membered ring. However, it was postulated that a substrate such as **286** with appropriately functionalized groups at C-8 and C-9 would allow the use of a ring closing metathesis strategy. With this idea in mind, it was decided to install a (2-*tert*-butyldimethylsiloxy)ethyl group at C-9 since it would potentially allow access to two olefins (**288** or **289**) that could be used to construct the seven membered ring through a ring closing metathesis (**Scheme 3.49**). The nature of the R_1 group at C-8 of **287** was left undefined at this stage. This issue would be revisited if the

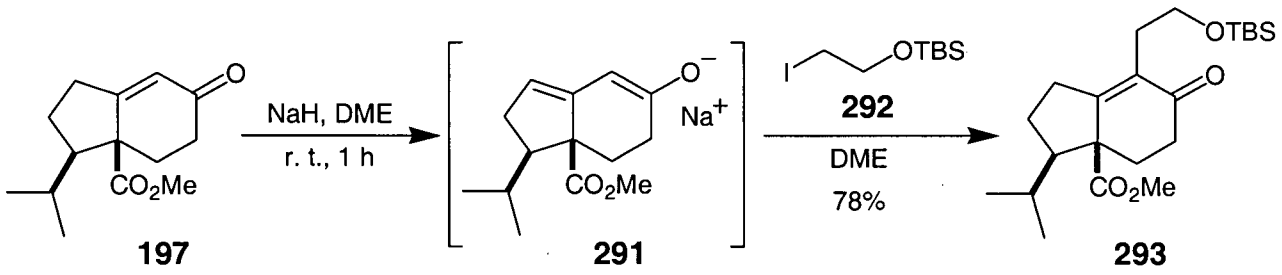
installation of the carbon chirality centers at C-8, C-9 and C-10 with the correct relative configuration could be accomplished as planned. Thus, for the time being, epoxide **290** became the synthetic target (see **Scheme 3.49**).



Scheme 3.49: Potential conversion of the (2-*tert*-butyldimethylsiloxy)-ethyl group of 287 to an allyl group in 288 or a vinyl group in 289

3.4.4.2 Third synthetic approach to (±)-isomulinic acid

The first step in this new synthetic strategy involved the preparation of enone **293**. This operation was accomplished by forming the thermodynamic extended sodium enolate of alkene **197** in DME, and quenching it with an excess of iodide **292**[142] (**Scheme 3.50**).



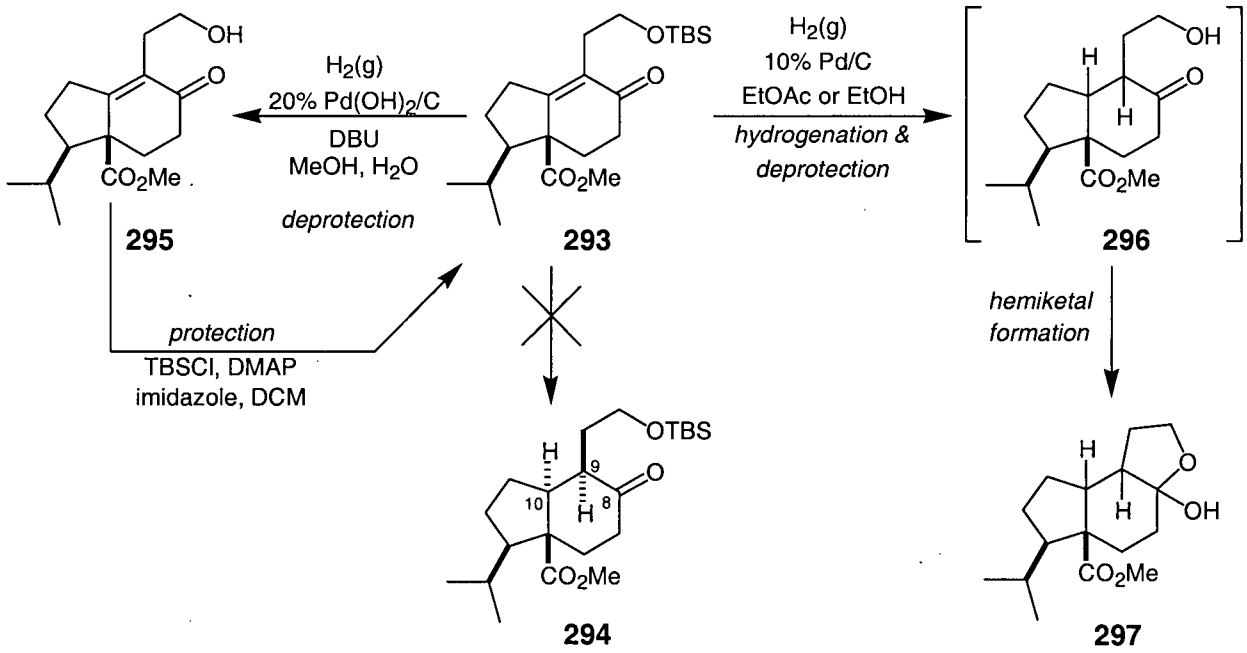
Scheme 3.50: Synthesis of enone 293

The spectral data collected on enone **293** verified its structure. The incorporation of the side chain was evidenced by the appearance of two three-proton singlets at $\delta = -0.02$ and -0.04 and a nine-proton singlet at $\delta = 0.83$ in the ^{1}H NMR spectrum, which correspond to the *tert*-butyldimethylsiloxy moiety. In addition, a two-proton multiplet at $\delta = 3.50$-3.64 was assigned to the methylene group attached to oxygen. The ^{13}C NMR spectrum showed the correct number of signals. A *J*-mod ^{13}C NMR experiment demonstrated the presence of six methylene groups and a total of ten methyl and methine groups. Furthermore, the molecular formula of enone **293** was verified by an HRMS measurement of its parent ion.

Access to enone **293** set the stage for the heterogenenous hydrogenation that was expected to provide the *trans*-fused ketone (**294**) with the correct relative configuration at C-10 (mulinane numbering, see **Scheme 3.51**). Overman[143] has reported heterogeneous hydrogenation conditions which allow the *in situ* epimerization of the carbon chirality center α to the carbonyl group. Treatment of enone **293** with $Pd(OH)_2/C$ in the presence of DBU under hydrogen at one atmosphere provided a polar, UV-active material. This material was determined to be enone **295** on the basis

of ^{1}H NMR and GC-LRMS data. Enone **293** could be obtained from **295** under standard protection conditions, thereby confirming the structure of the latter compound.

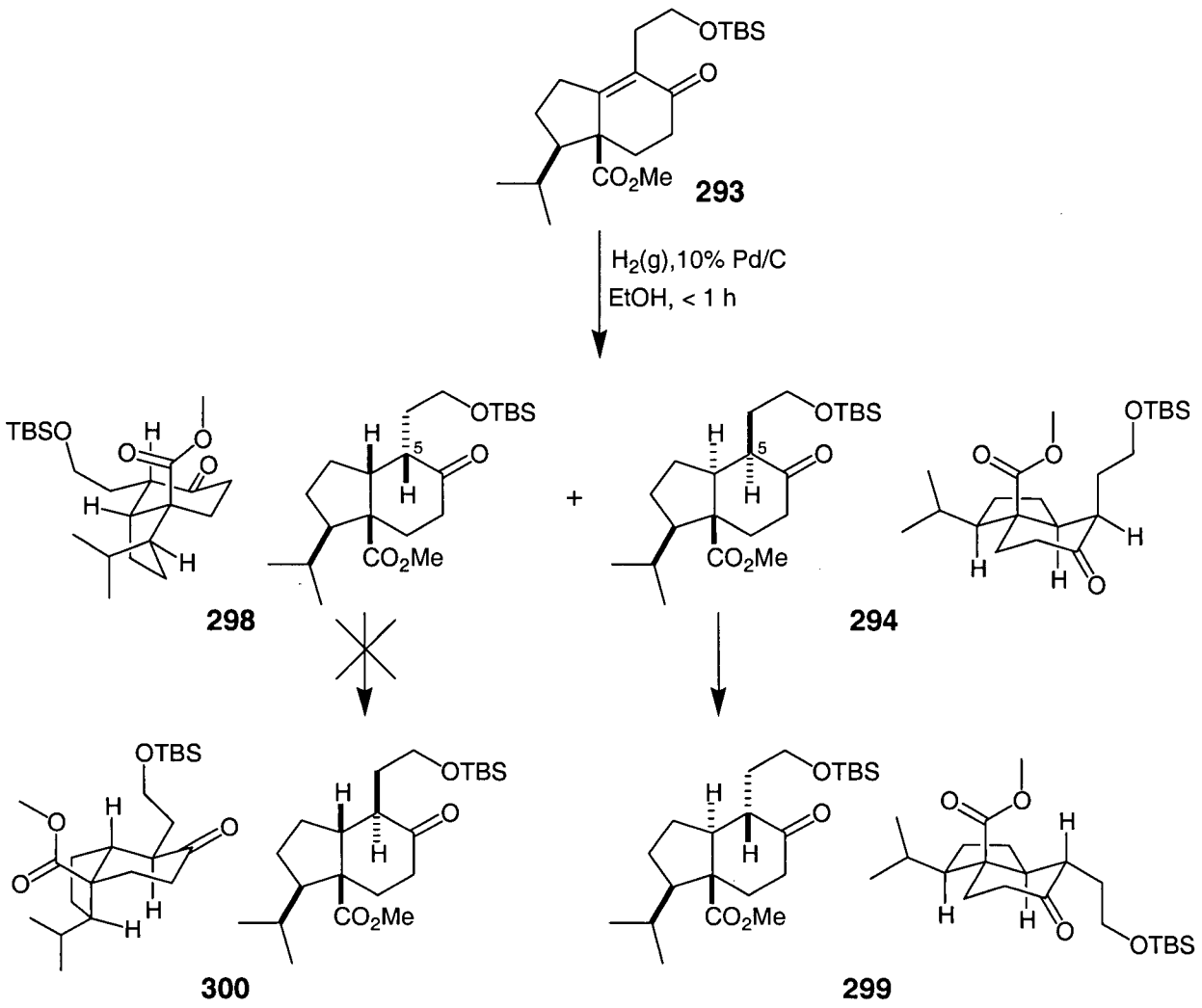
Alternatively, treatment of enone **293** with a catalytic amount of Pd/C under hydrogen at one atmosphere provided two main products (**Scheme 3.51**). TLC analysis of the reaction mixture showed that these materials did not absorb ultraviolet light (λ = 254 nm). Their ^{1}H NMR spectra revealed that the *tert*-butyldimethylsilyl group had been removed under the hydrogenation conditions. Analysis of the products by GC-LRMS showed that their molecular mass is consistent with the structure of hydroxy ketones **296** or their corresponding hemiketals **297**. Attempts to re-protect the hydroxyl group (as had been done with enone **295**) failed, and thus indicated that hemiketals **297** had been formed. This type of hemiketal formation has been previously reported by Molander.[144] The failure to protect the alcohol also indicated that no equilibrium exists between hydroxyketone **296** and hemiketal **297** under the conditions used for protection of the primary alcohol.



Scheme 3.51: Attempted hydrogenation of enone 293 to ketone 294 under heterogenenous conditions

It was hypothesized that the formation of hemiketals **297** occurred through the initial hydrogenation of the double bond, followed by deprotection of the alcohol and subsequent hemiketal formation. This suggested that the hydrogenation of **293** should be carried out using a large amount of palladium-on-carbon in order to increase the rate of the reaction. Indeed, this hydrogenation was complete in less than one hour and furnished three products (**Scheme 3.52**). GC-LRMS analysis of the mixture of products showed that their molecular masses were consistent with the structures of compounds **294**, **298** and **299**.

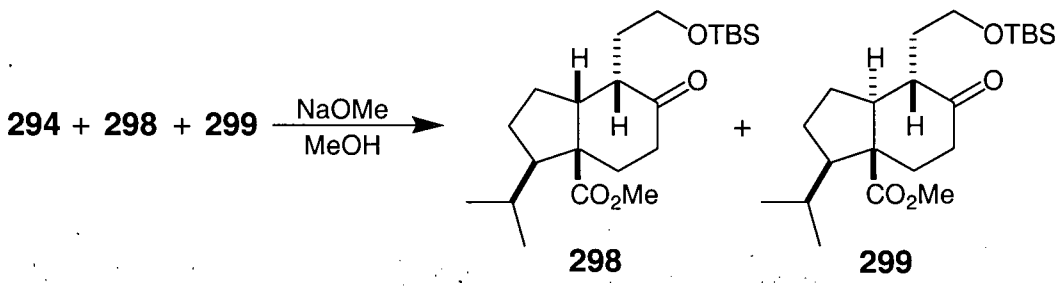
According to the mechanistic rationale presented in **Scheme 3.46**, the hydrogenation of enone **293** should provide, initially, two diastereomeric ketones in which the newly incorporated hydrogen atoms have a *cis* relationship to each other (**294** and **298** in **Scheme 3.52**). The *cis*-fused product (**298**) may adopt a conformation in which the alkyl group at C-5 resides in the equatorial position. It is conceivable that ketone **298** would isomerize to its C-5 epimer (**300**) under thermodynamic conditions. Ketone **300** can also adopt a conformation in which the C-5 alkyl group lies in the equatorial position.



Scheme 3.52: Hydrogenation of enone 293, formation of ketones 294, 298 and 299

The initially formed *trans*-fused product (**294**) is conformationally locked, and therefore, the C-5 alkyl group resides in the axial position. The severe 1,3-diaxial steric interaction between the alkyl group and the methoxycarbonyl present in ketone **294** makes it less stable relative to its C-5 epimer (**299**). In theory, this should allow for the complete conversion of ketone **294** to ketone **299** under equilibrating conditions.

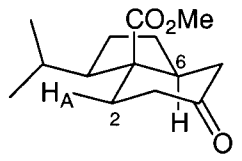
Subjection of a mixture of ketones **294**, **298** and **299** to epimerization conditions resulted in the complete conversion of ketone **294** to ketone **299**. Ketone **298** remained unchanged.



Scheme 3.53: Equilibration of ketones 294, 298 and 299

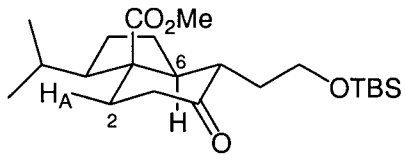
The IR spectrum of ketone **299** displayed two strong carbonyl stretching absorptions at 1712 and 1724 cm^{-1}. The mass spectrum did not display an M^+ ion, however, an HRMS measurement of the $[M–t\text{-}Bu]^+$ ion verified the molecular formula. The ^1H NMR and ^{13}C NMR spectra displayed the correct number of signals. A *J*-mod ^{13}C NMR spectrum verified the presence of six methylene groups and a total of twelve methyl and methine groups.

The results obtained from the hydrogenation and epimerization reactions shown in **Schemes 3.52** and **3.53** demonstrated that ketone **299** was indeed the desired material. No further efforts to ascertain the relative configuration at C-5 were made. However, comparison of the ^1H NMR data obtained for ketone **299** with that obtained for ketone **249**, particularly the signal corresponding to the equatorial proton at C-2, indicated that the configuration at C-6 was as desired (see **Figure 3.23**).



249

H_A: δ = 2.75-2.83 (ddd, *J* = 13.1, 6.8, 1.8 Hz)



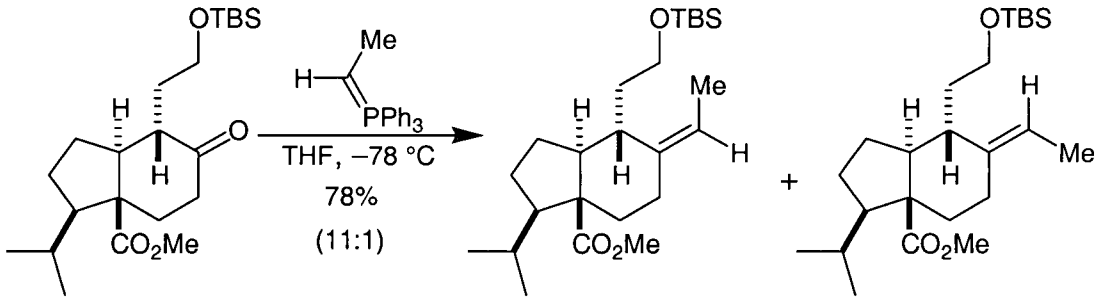
299

H_A: δ = 2.73-2.83 (ddd, *J* = 13.1, 6.7, 2.1 Hz)

Figure 3.23: Comparison of ^1H NMR data for ketone 249 with ^1H NMR data for ketone 299

Unfortunately, attempts to carry out the hydrogenation of enone **293** in large scale always resulted in the formation of undesired sideproducts (**297**, see **Scheme 3.51**). Rather than trying to optimize the hydrogenation process at this stage, it was decided to proceed with the synthetic plan using the amount of ketone **299** acquired thus far.

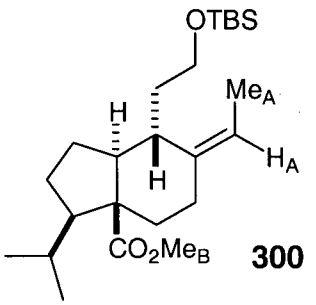
The next step in the sequence involved the preparation of alkenes **300** and **301** from ketone **299** through the use of a Wittig protocol. In the event, an 11:1 mixture of alkenes **300** and **301** were obtained in 78% overall yield. The geometry about the double bond in the major product was determined to be as shown using a number of ^{1}H NMR experiments on a derivative of **300** (see **Tables 4.18** and **4.19** in the experimental section).



299 **300** **301**

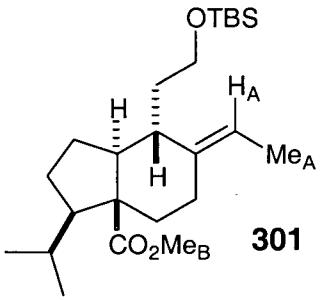
Scheme 3.54: Preparation of alkenes 300 and 301

Unfortunately, the acquired mixture of alkenes proved inseparable by flash column chromatography on silica gel, and this prevented their full characterization. However, the ^{1}H NMR spectrum obtained on the mixture did show the expected signals for the two products (**Figure 3.24**).



300

H_A: δ = 5.17 (q; *J* = 6.8 Hz)
Me_A: δ = 1.46 (d; *J* = 6.8 Hz)
Me_B: δ = 3.53 (s)



301

H_A: δ = 5.11 (q; *J* = 6.7 Hz)
Me_A: δ = 1.45 (d; *J* = 6.7 Hz)
Me_B: δ = 3.60 (s)

Figure 3.24: Selected ^{1}H NMR data for alkenes 300 and 301

The synthetic plan called for the treatment of alkenes **300** and **301** with a suitable oxidant in order to establish the epoxide moiety. Based on the calculated structure of the transition state for the oxidation of alkenes by DMDO,[145,146] the epoxidation was expected to occur through the approach of the oxidant from the β-face of the alkene, as shown in **Figure 3.25**. Indeed, Johnson *et al.*[147] have stated that during the oxidation of methylenecyclohexanes "the effect of steric hydrance favours, obviously, the equatorial attack." At the time, it was not conceived that the planned epoxidation of alkene **300** would be subject to any stereoelectronic effects.[147]

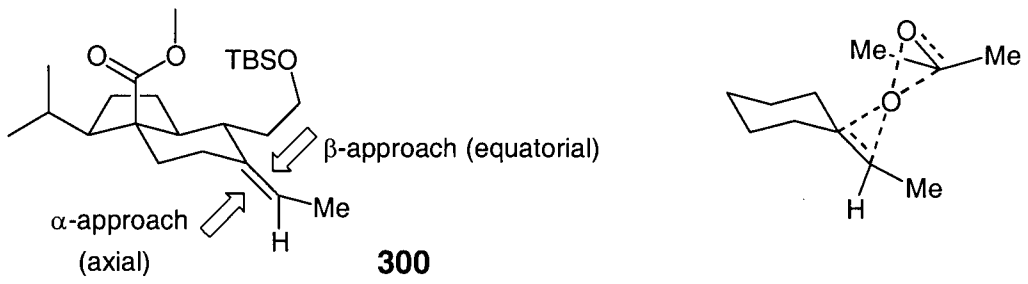
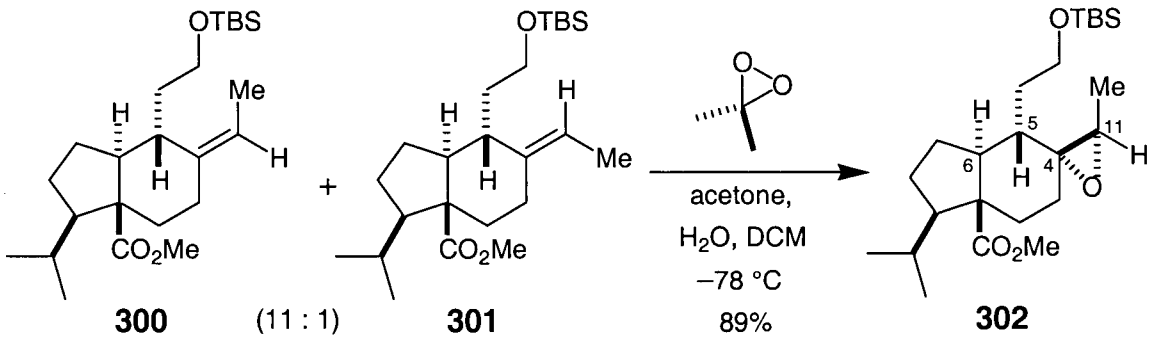


Figure 3.25: Two possible approaches to the double bond of alkene 300 by an oxidant and expected shape of the transition state for the epoxidation of methylenecyclohexane by DMDO under steric control

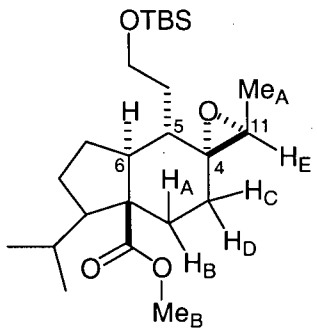
The dimethyldioxirane (DMDO) mediated epoxidation of alkenes **300** and **301** furnished a mixture of products which were easily separated by flash column chromatography on silica gel (**Scheme 3.55**). The structure of the major product was determined to be as shown in **302** (see **Tables 4.18** and **4.19** in the experimental section for details). No effort was made to isolate or characterize the minor product.



Scheme 3.55: Epoxidation of alkenes 300 and 301

The ^{1}H NMR spectrum of epoxide **302** exhibited a three-proton doublet at $\delta =$ 1.08 and a one-proton quartet at $\delta =$ 2.67-2.72 with a mutual coupling constant of 5.4 Hz. These signals could be assigned to the proton and the methyl group on the epoxide ring. The ^{13}C NMR spectrum displayed a quaternary carbon signal at $\delta = 63.4$ and a methine carbon signal at $\delta = 61.8$, which correspond to the two epoxide carbons. The molecular formula of epoxide **302** was verified through an HRMS measurement of its parent ion.

A full suite of NMR experiments were performed on a sample of epoxide **302** and allowed the complete assignment of its structure (see **Tables 4.18** and **4.19** in the experimental section). A number of 1D selective NOE difference experiments established the configuration of the carbon chirality centers at C-4 and C-11 (**Figure 3.26**). These experiments also served to indirectly determine the geometry of the double bond in alkene **300**.



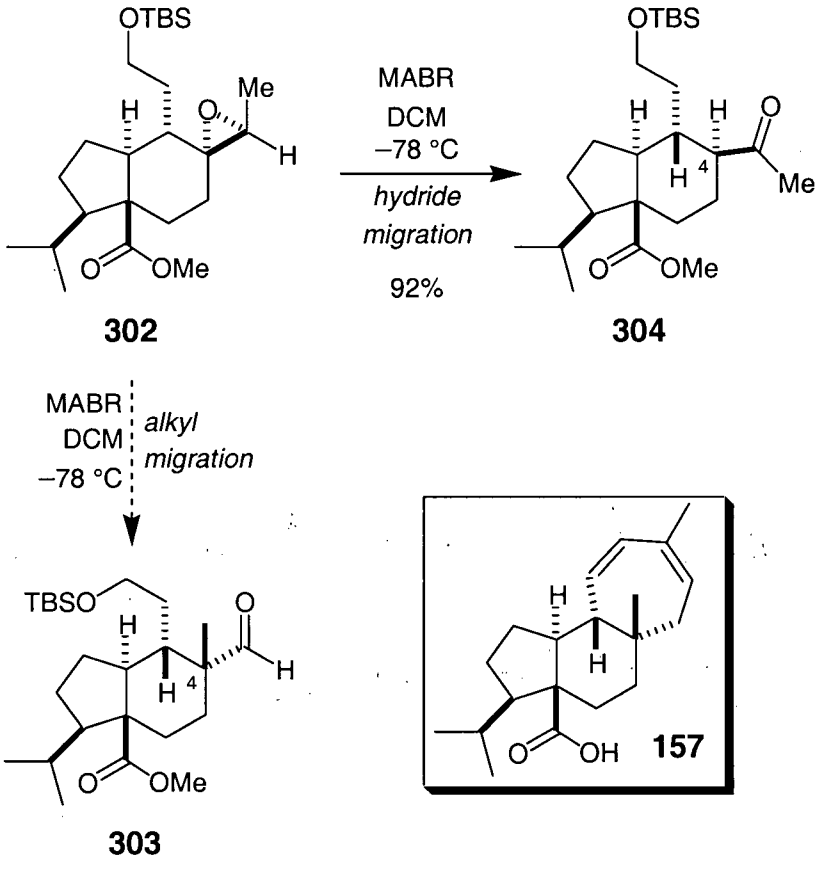
302

H$_A$: δ = 1.45-1.52 (dd; 13.7, 10.3 Hz)
H$_B$: δ = 2.70-2.79 (ddd; 13.7, 9.3, 9.3 Hz)
H$_C$: δ = 0.90-0.98 (dd; 13.4, 9.3 Hz)
H$_D$: δ = 2.67-2.72 (ddd; 13.4, 10.3, 9.3 Hz)
H$_E$: δ = 2.14-2.22 (ddd; 5.4, 5.4, 5.4 Hz)
Me$_A$: δ = 1.08 (d; 5.4 Hz)
Me$_A$: δ = 3.65 (s)

Irradiation of H$_B$ enhances H$_A$ and H$_C$
Irradiation of H$_D$ enhances H$_C$ and H$_A$
Irradiation of H$_E$ enhances H$_C$
Irradiation of Me$_A$ enhances Me$_B$ and H$_E$

Figure 3.26: Selected NOE difference data for epoxide 302

Note that epoxide **302** does not possess the desired relative configuration at C-4. This meant that the synthetic plan outlined in section **3.4.4.1** would not yield access to the mulinane family of diterpenoids. However, if treatment of epoxide **302** with MABR promoted the migration of the methyl group to C-4, aldehyde **303** would be obtained (**Scheme 3.60**). Note that aldehyde **303** has the correct relative configuration at all the carbon chirality centers present in **157**. Furthermore, the aldehyde moiety could potentially be used to install an alkenyl chain which would participate in a ring-closing metathesis reaction to establish the seven-membered ring.

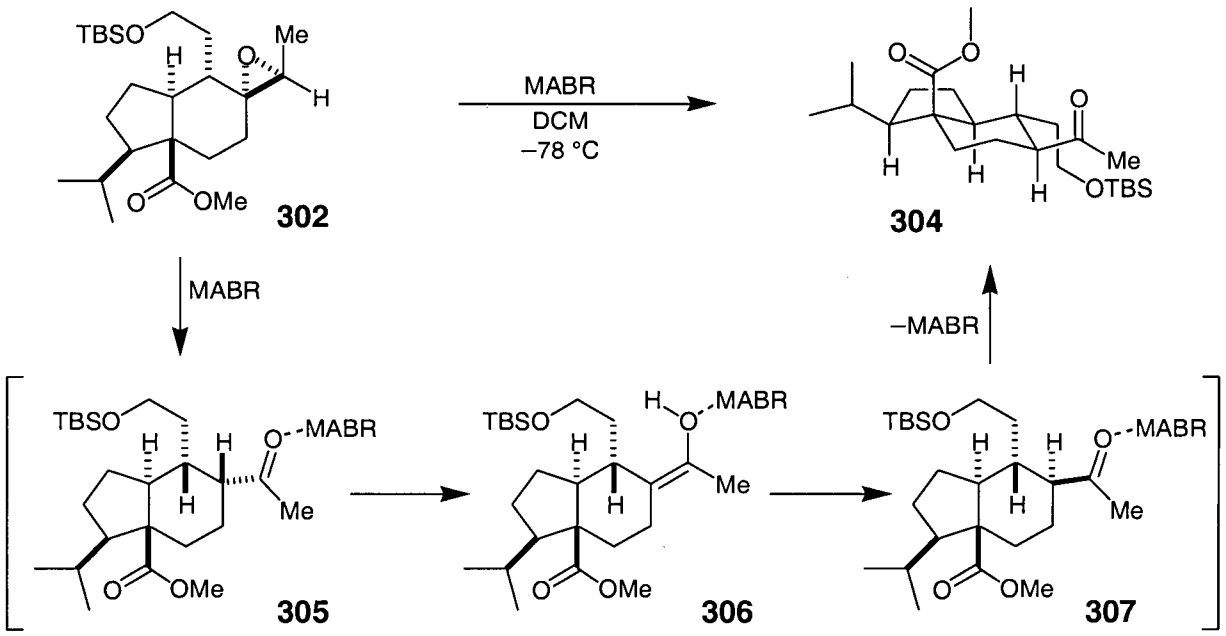


Scheme 3.60: Lewis acid mediated rearrangement of epoxide 302

Unfortunately, treatment of epoxide **302** with a stoichiometric amount of MABR[140] resulted in the formation of methyl ketone **304** in excellent yield (**Scheme 3.60**). The ^{1}H NMR spectrum of **304** displayed a three-proton singlet at $\delta = 2.07$ that was attributed to the methyl ketone group. In addition, a signal at $\delta = 2.24\text{-}2.34$ (ddd, 1 H, $J = 12.6, 11.0, 4.3$ Hz) was assigned to the axial proton at C-4. The ketone carbonyl carbon appeared at $\delta = 212.5$ in the ^{13}C NMR spectrum. The IR spectrum clearly displayed two carbonyl stretch absorptions at 1724 and 1712 cm^{-1}, which correspond to the ester and the ketone groups, respectively. Finally, the molecular formula for ketone **304** was verified through an HRMS measurement of its parent ion.

Based on significant literature precedent, the rearrangement of epoxide **302** with migration of the hydride was expected to provide ketone **305**. However, ketone **304** was observed as the single product of this reaction. This indicated that the Lewis acid

also catalyzed the epimerization of the initially formed ketone (see **Scheme 3.61**). In order to confirm that the acetyl group resides in the equatorial position, a solution of **304** in NaOMe/MeOH was allowed to stir for two days at room temperature. The product isolated from this reaction was identical to the starting material.



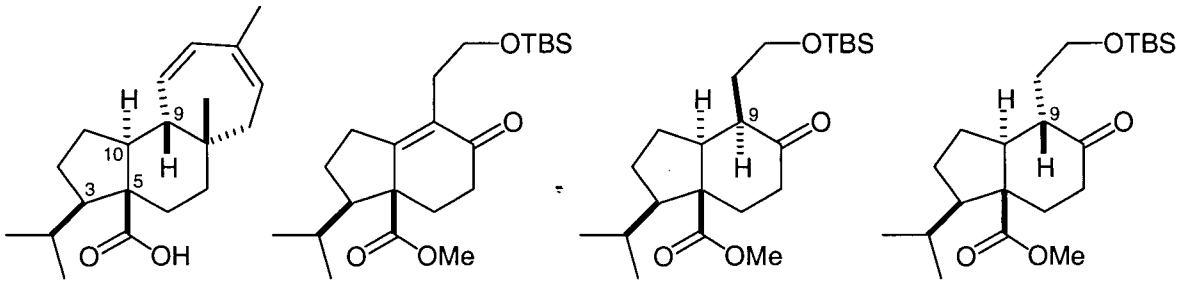
Scheme 3.61: Pathway for the MABR catalyzed rearrangement of epoxide 302 to ketone 304

Clearly, this synthetic plan would not provide access to the mulinane family of diterpenoids. However, it seemed likely that, after some modifications, the heterogeneous hydrogenation of enone **293** or a similar substance would provide efficient and expedient access to a bicyclic system with the correct relative configuration at four of the five carbon chirality centers found in the mulinane carbocyclic system. Thus, a new synthetic strategy that incorporated the heterogeneous hydrogenation of an α-alkyl enone was devised.

3.4.5 Fourth synthetic approach to (±)-isomulinic acid

3.4.5.1 Retrosynthetic analysis

The work described in section **3.4.4.2** demonstrated that the hydrindane system embedded in the mulinane diterpenoids (see **157**, **Figure 3.27**), with the correct relative configuration at C-3, C-5, C-9 and C-10, could be obtained in an expedient fashion from enone **293**. This process involved the hydrogenation of enone **293** under heterogeneous conditions to provide ketone **294**. This material, in turn, allowed access to ketone **299** after epimerization of the carbon chirality center at C-9.



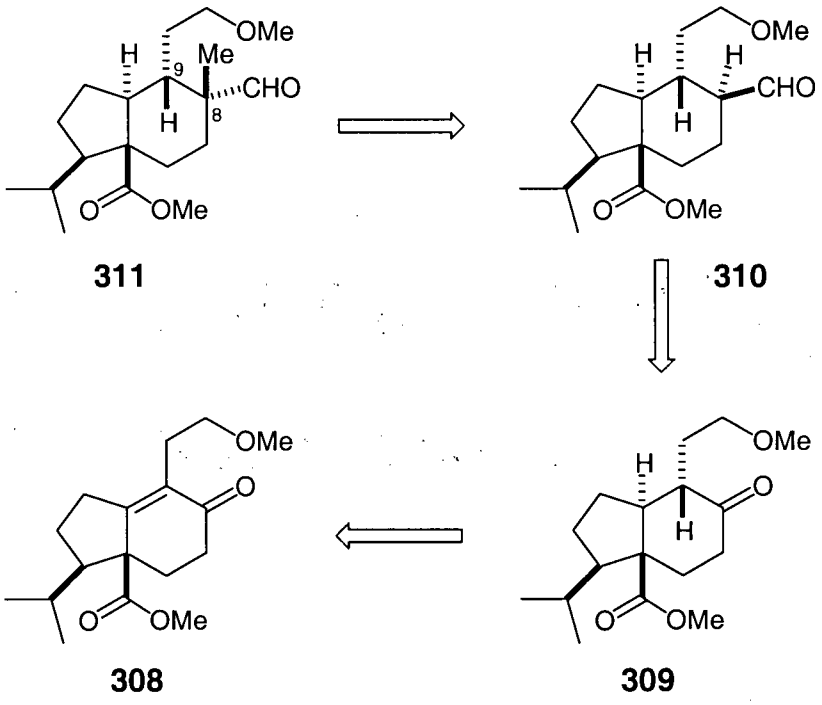
157 **293** **294** **299**

Figure 3.27: Structures of mulin-11,13-dien-20-oic acid (157), enone 293 and ketones 294 and 299

Unfortunately, the hydrogenation process could not be scaled up without the generation of undesired sideproducts. It appeared likely that replacing the *tert*-butyldimethylsilyl group of enone **293** with a more stable protecting group would allow for the efficient generation of a bicyclic system analogous to **299** in large scale. Therefore, it was decided to protect the primary alcohol as a methyl ether (as in **308**, **Scheme 3.62**) since this group is stable under a variety of conditions. This would allow access to a system such as **309** using the same hydrogenation and epimerization sequence.

The installation of the methyl group at C-8 was envisioned to occur through the alkylation of aldehyde **310** or a derivative thereof. The relative configuration of the

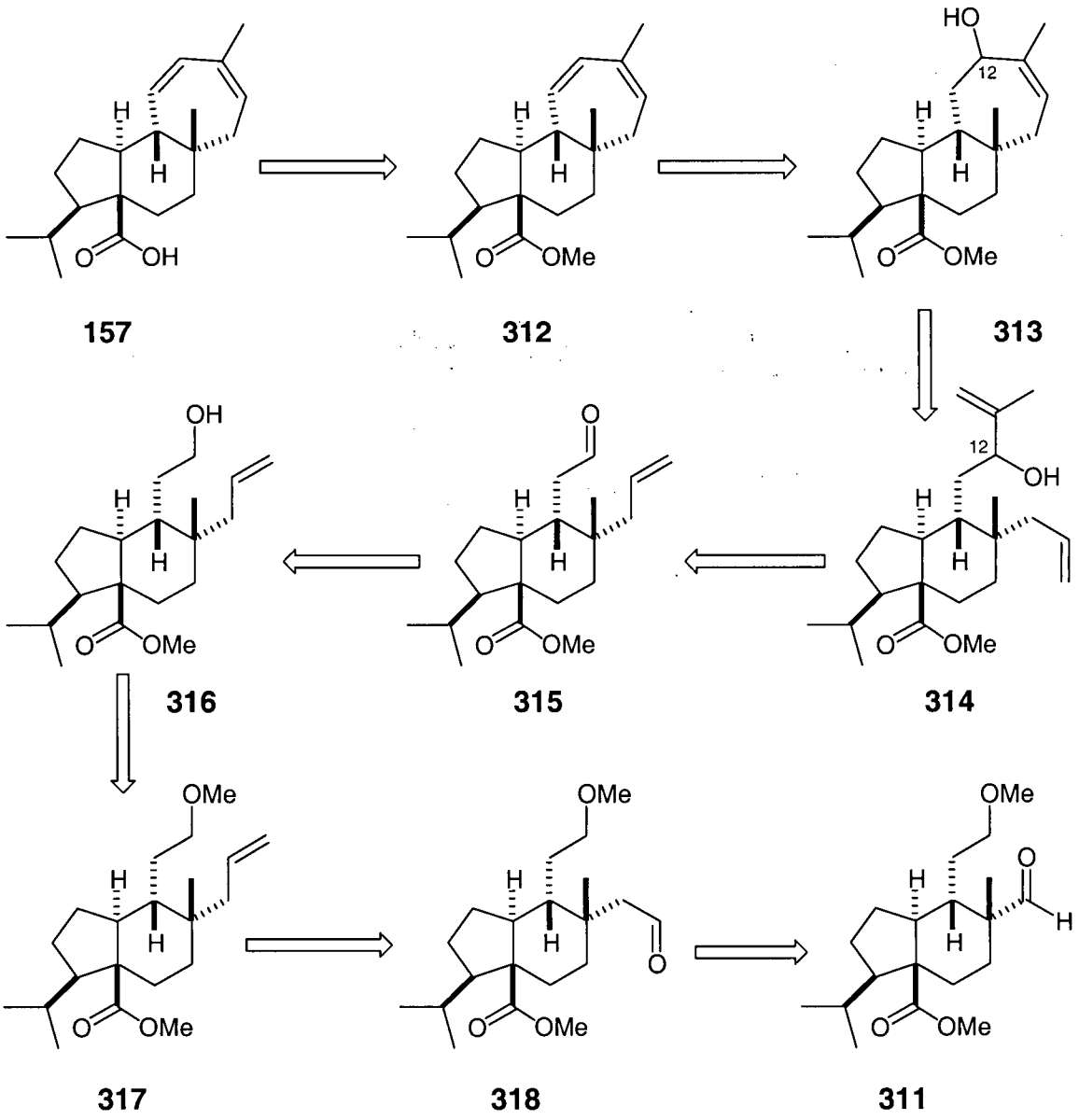
carbon chirality center at C-8 was expected to be as shown in **311** based on significant literature precedent. Aldehyde **310** would be prepared from ketone **309** using standard methods.



Scheme 3.62: Retrosynthesis of aldehyde 311 to enone 308

It appeared likely that the aldehyde group at C-8 and the 2-methoxyethyl group at C-9 of aldehyde **311** could be transformed into two alkenyl chains that would participate in a ring-closing metathesis reaction. Therefore, the retrosynthetic analysis for the construction of compound **157** from aldehyde **311** was based on the use of a ring-closing metathesis as a key step (**Scheme 3.63**). Compound **157** should be accessible from diene **312** upon conversion of the ester group to the corresponding acid. Dehydration of allylic alcohol **313** would furnish diene **312**. Allylic alcohol **313** was expected to be the major product of the crucial ring-closing metathesis reaction utilizing diene **314** as the substrate. Compound **314** would be accessed upon alkylation of aldehyde **315** with a suitable Grignard reagent. Note that the relative configuration of the carbon chirality center at C-12 of allylic alcohol **314** does not need to be defined at any stage since both isomers should eventually lead to diene **312**. The oxidation of alcohol **316** to the corresponding aldehyde was expected to occur under

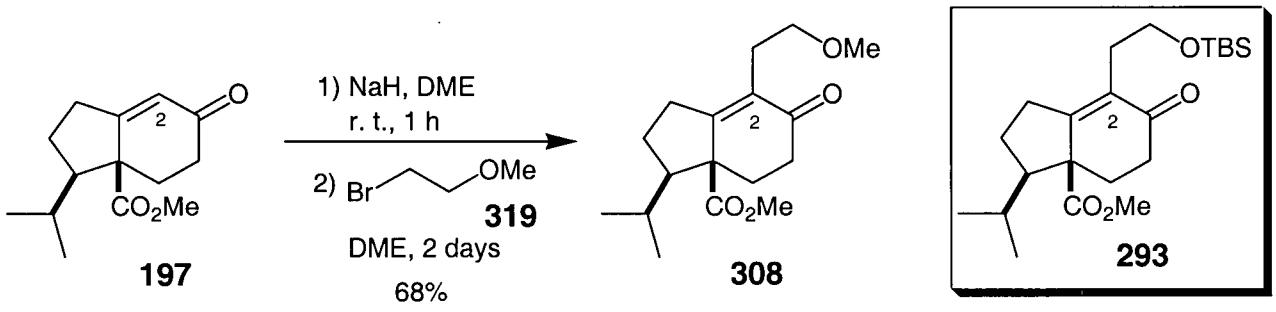
standard conditions. It was envisioned that the conversion of methyl ether **317** to primary alcohol **316** would take place under the action of BBr_3[148,149] or TMSI.[150] The homologation of aldehyde **311** to aldehyde **318**, and the subsequent conversion of aldehyde **318** to alkene **317** was expected to occur under standard conditions.



Scheme 3.63: Retrosynthesis of mulin-11,13-dien-20-oic acid (157) to aldehyde 311

3.4.5.2 Fourth synthetic approach to (±)-isomulinic acid

The first step in the present strategy involved the installation of the 2-methoxyethyl group at C-2 of enone **197**. This operation was accomplished using conditions similar to those used to prepare enone **293** (see **Scheme 3.64** and **Scheme 3.50**). Thus, treatment of enone **197** with NaH in DME provided the thermodynamic sodium enolate. The alkylation of this enolate with 2-bromoethyl methyl ether (**319**) occurred at a slow rate and in good yield.

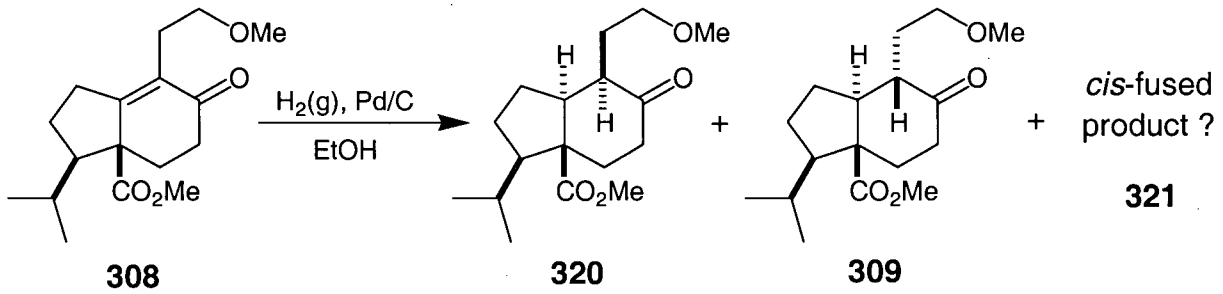


Scheme 3.64: Synthesis of enone 308

The IR spectrum of enone **308** displayed two carbonyl stretching absorptions at 1665 and 1725 cm^{-1}, which were attributed to the α,β-unsaturated ketone and the methyl ester group, respectively. The ^1H NMR spectrum displayed the correct number of signals, including a three-proton singlet at $\delta = 3.24$, which was attributed to the newly introduced methyl ether. In addition, a two-proton multiplet at $\delta =$ 3.25-3.32 was attributed to the methylene group adjacent to the ether oxygen atom. The ^{13}C NMR spectrum displayed the correct number of signals, including two alkenyl carbon signals at $\delta = 129.9$ and $\delta = 167.9$. A *J*-mod ^{13}C NMR experiment demonstrated the presence of six methylene groups and a total of six methyl and methine groups. The molecular formula of enone **308** was verified by an HRMS measurement of its parent ion.

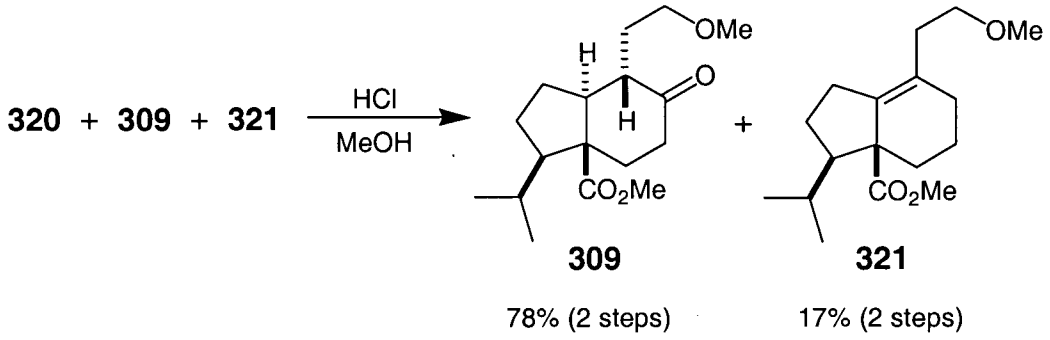
Access to enone **308**, set the stage for the proposed heterogeneous hydrogenation reaction that was expected to establish the correct relative configuration of the carbon chirality center at C-6 of ketone **308**. Treatment of enone **308** with a catalytic amount of 10% palladium-on-carbon under hydrogen at one atmosphere

provided a mixture of three products. At this stage the nature of the products was not determined, but was hypothesized to be as shown in **Scheme 3.65** based on the mechanistic rationale outlined in **Scheme 3.46** and the results obtained for the homogeneous hydrogenation of enone **293** (see **Scheme 3.52**).



Scheme 3.65: Heterogeneous hydrogenation of enone 308.

Treatment of the mixture of compounds **320**, **309** and **321** with HCl in MeOH resulted in the convergence of compounds **320** and **309** into **309**. Compound **321** remained unchanged (**Scheme 3.66**). At this stage compounds **309** and **321** were easily separated using flash column chromatography on silica gel.

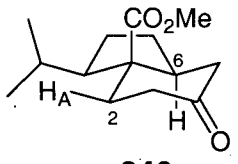


Scheme 3.66: Equilibration of a mixture of compounds 320, 309 and 321

The spectroscopic data collected on compound **309** was consistent with the assigned structure. The IR spectrum showed that the two carbonyl stretching absorptions coincided at 1723 cm^{-1}. The ^{1}H NMR spectrum displayed the correct number of signals. A *J*-mod ^{13}C NMR spectrum demonstrated the presence of six

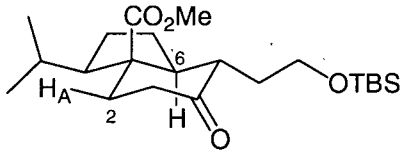
methylene groups and a total of eight methyl and methine groups. In addition, its molecular formula was verified through the HRMS measurement of its parent ion.

The relative configuration of the newly formed carbon chirality centers at C-5 and C-6 of ketone **309** was not determined spectroscopically at this stage. However, comparison of the ^{1}H NMR data collected on ketone **309** with that collected for ketones **249** and **299** indicated that the relative configuration at C-5 was as desired (**Figure 3.28**).



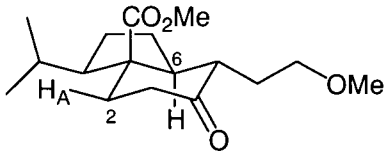
249

H_A: δ = 2.75-2.83 (ddd, *J* = 13.1, 6.8, 1.8 Hz)



299

H_A: δ = 2.73-2.83 (ddd, *J* = 13.1, 6.7, 2.1 Hz)

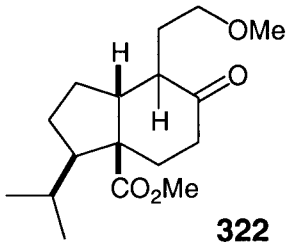


309

H_A: δ = 2.74-2.83 (ddd, *J* = 13.0, 6.7, 2.2 Hz)

Figure 3.28: Comparison of ^{1}H NMR data for ketones 249 and 299 with ^{1}H NMR data for ketone 309

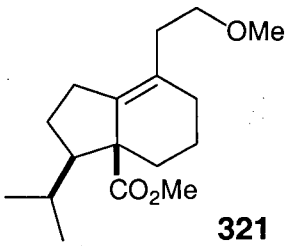
The structure of compound **321** was assigned to be as shown in **Scheme 3.66** based on the spectroscopic data collected. The IR spectrum showed a carbonyl stretching absorption at 1723 cm^{-1}. The ^{1}H NMR spectrum displayed the correct number of signals. Taken together, these data cannot be used to differentiate between compound **321** or the *cis*-fused ketone **322** (see **Figure 3.29**). However, an HRMS measurement of the parent ion of compound **321** indicated its molecular formula to be as shown in **Figure 3.29**. The ^{13}C NMR spectrum displayed two resonances at δ = 139.0 and δ = 126.7, which indicated the presence of a carbon-carbon double bond in the molecule. No resonances corresponding to a ketone carbonyl were observed. Furthermore, a *J*-mod ^{13}C NMR experiment showed that compound **321** possesses seven methylene groups and a total of six methyl and methine groups.



322

$C_{17}H_{28}O_4$

CH_1: 4
CH_2: 6
CH_3: 4



321

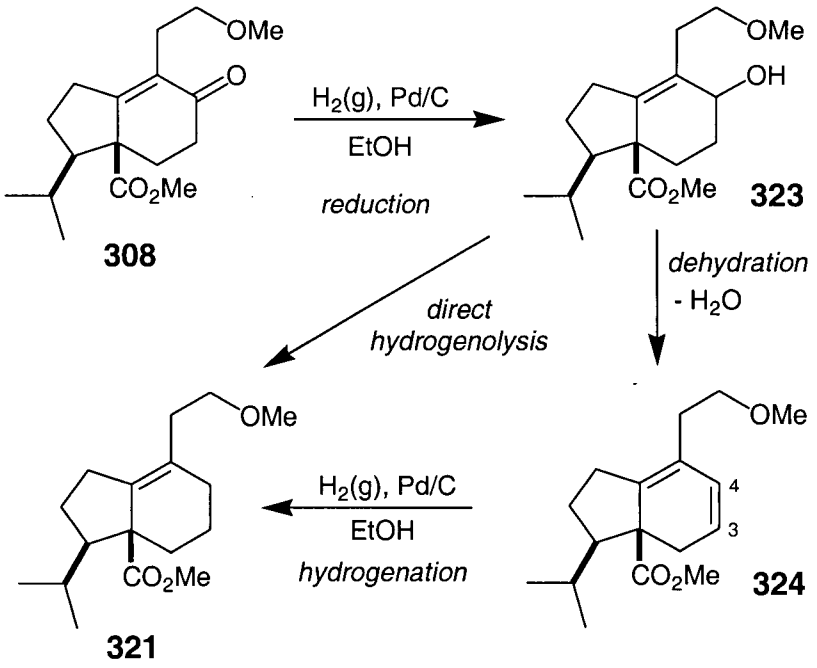
$C_{17}H_{28}O_3$

CH_1: 2
CH_2: 7
CH_3: 4

Figure 3.29: Selected structural data expected for ketone 322 and alkene 321

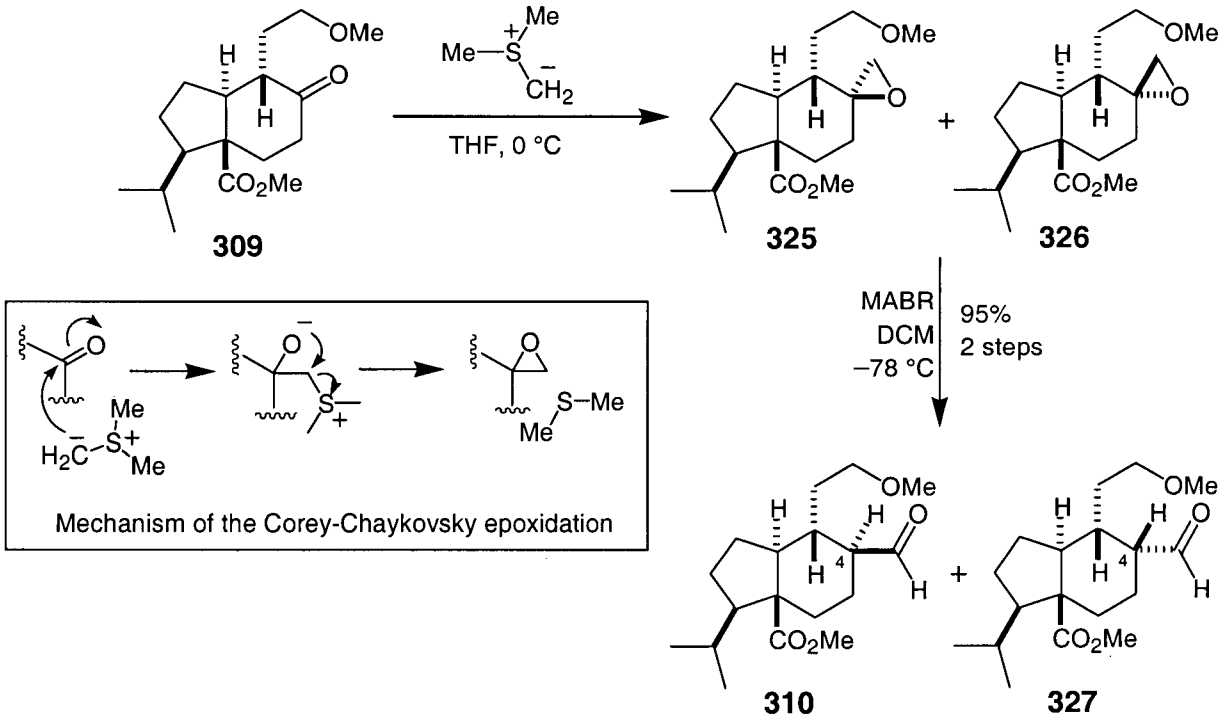
The generation of alkene **321** as the major side-product from the heterogeneous hydrogenation of enone **308** requires some comment. A proposed pathway for this transformation is presented in **Scheme 3.67**. The reduction of cyclic ketones to secondary alcohols is known to proceed under heterogeneous conditions using dispersed metals, including palladium, as catalysts.[151] Therefore, it is possible that some of enone **308** would provide allylic alcohol **323** during the hydrogenation reaction. Alcohol **323** is prone to dehydration to provide diene **324**. Finally, the hydrogenation of the carbon-carbon double bond between C-3 and C-4 of diene **324** would furnish alkene **321**.

Although conceivable, it is unlikely that alkene **321** would arise through the direct hydrogenolysis of alcohol **323** since forcing conditions (high pressure and temperature) are usually required for this process.[152]



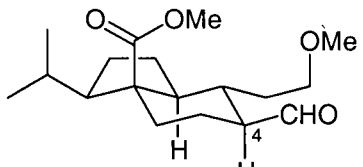
Scheme 3.67: Proposed mechanism for the generation of alkene 321 from enone 308 under heterogeneous hydrogenation conditions.

The synthetic plan called for the conversion of ketone **309** to aldehyde **310**. This transformation was efficiently accomplished in two steps (**Scheme 3.68**). Ketone **309** was converted to a mixture of spiroepoxides **324** and **325** using the method developed by Corey and Chaykovsky[153-155] (see inset, **Scheme 3.68**) and the conditions reported by Danishefsky.[156] These epoxides proved inseparable by flash column chromatography on silica gel. The mixture of epoxides was treated with a Lewis acid (**MABR**, see **Scheme 3.47**), which promoted the rearrangement of the epoxide moiety to the corresponding aldehyde.[140] The mechanism of this rearrangement is similar to that previously discussed in **Scheme 3.48**. Aldehydes **309** and **327** were also inseparable by flash column chromatography on silica gel, and were thus characterized as a mixture.



Scheme 3.68: Preparation of aldehydes 310 and 327 from ketone 309

Aldehydes **310** and **327** exist as a 3:1 mixture of C-4 epimers in HCl/$CDCl_3$. Although no efforts were made to ascertain the relative configuration of the carbon chirality center at C-4 of the two aldehydes, it is reasonable to expect the aldehyde group of the major isomer to reside in the equatorial position (see **Figure 3.30**). The IR spectrum of the mixture exhibited two carbonyl stretching absorptions at 1721 and 1704 cm^{-1}. The molecular formula was confirmed through an HRMS measurement of the parent ion. Both the ^{1}H NMR and ^{13}C NMR spectra showed resonances diagnostic of the aldehyde group (see **Figure 3.30**).

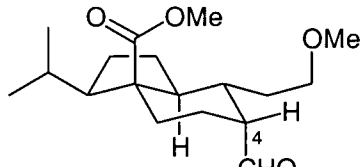


310

major (equatorial) epimer

^{13}C NMR: δ = 205.6

^{1}H NMR: δ = 9.85 (s)



327

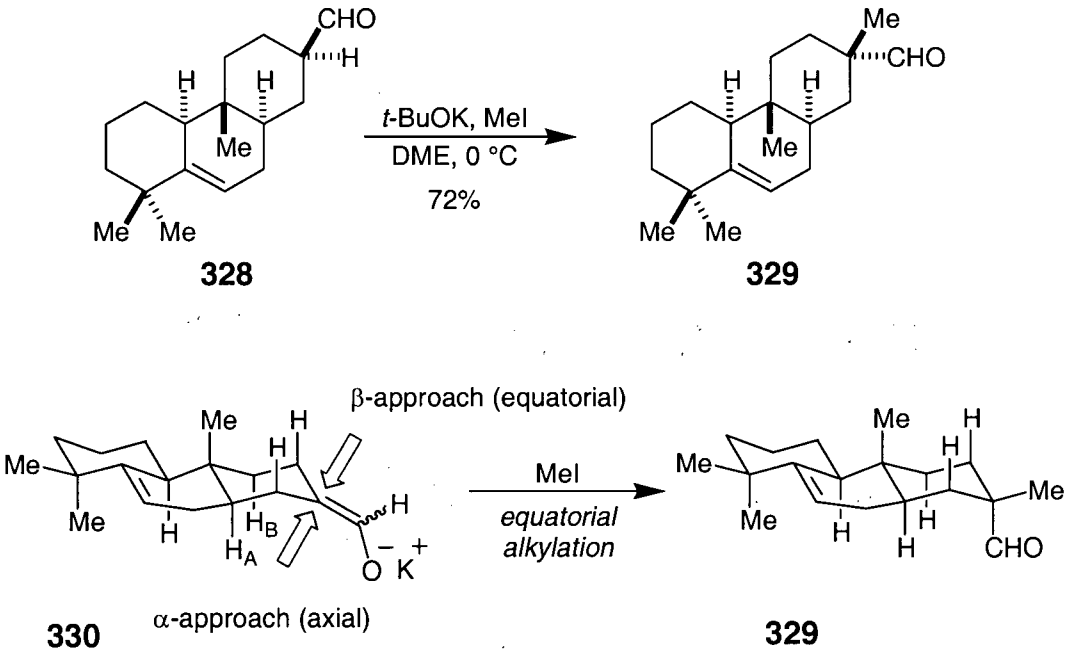
minor (axial) epimer

^{13}C NMR: δ = 204.5

^{1}H NMR: δ = 9.47 (d, J = 3.9 Hz)

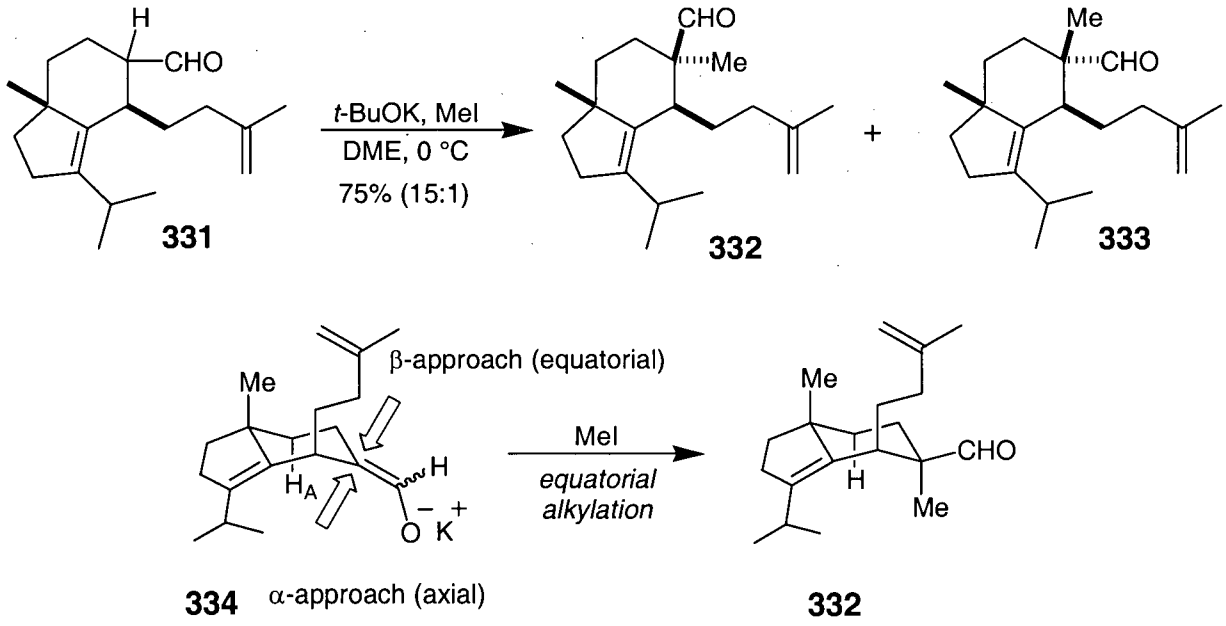
Figure 3.30: Selected spectral data for aldehydes 310 and 327

With aldehydes **309** and **327** in hand, the stage was set for the installation of the methyl group at C-4. Based on significant literature precedent,[120] the relative configuration of the new carbon chirality center was expected to be as desired. Ireland and Mander[157] have shown that the methylation of the potassium enolate of aldehyde **328** provides the axial aldehyde **329** as the sole product (**Scheme 3.69**). This high degree of diastereoselectivity has been attributed to the fact that the approach of the electrophile (MeI) to the α-face of the enolate (axial approach) is blocked by the two axial protons H_A and H_B (see **330**, **Scheme 3.69**). On the other hand, approach of the electrophile to the β-face of the enolate (equatorial approach) is unhindered.[158]



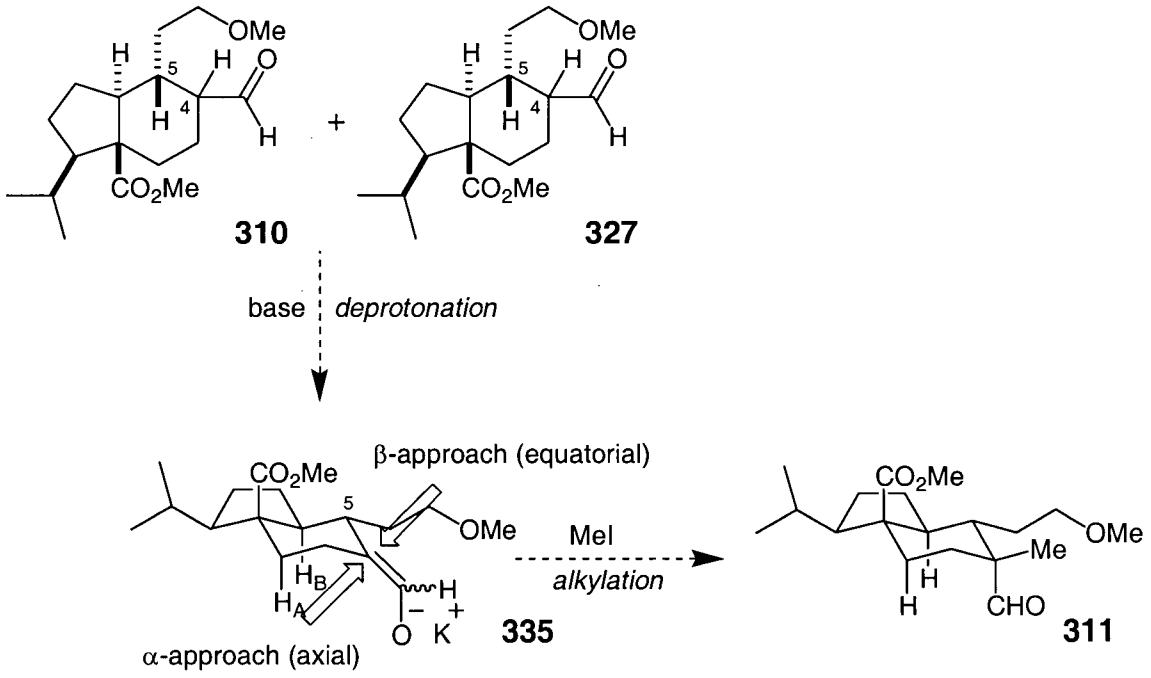
Scheme 3.69: equatorial alkylation of aldehyde 328 as shown by Ireland and Mander in a total synthesis of (±)-rimuene[157]

It must be noted that equatorial alkylation of exocyclic enolates is not always observed. Snider *et al.*[159] have shown that the alkylation of the potassium enolate of aldehyde **331**, generated using the same conditions used by Ireland and Mander, provided the equatorial aldehyde (**332**) as the major product (**Scheme 3.70**). In this example, the approach of the electrophile from the α-face of the enolate (axial approach) is only hindered by one axial proton (H_A) on the six-membered ring (see **334**). Furthermore, the approach of the electrophile from the β-face of the enolate (equatorial approach) is likely hindered by the axial isopentenyl chain.



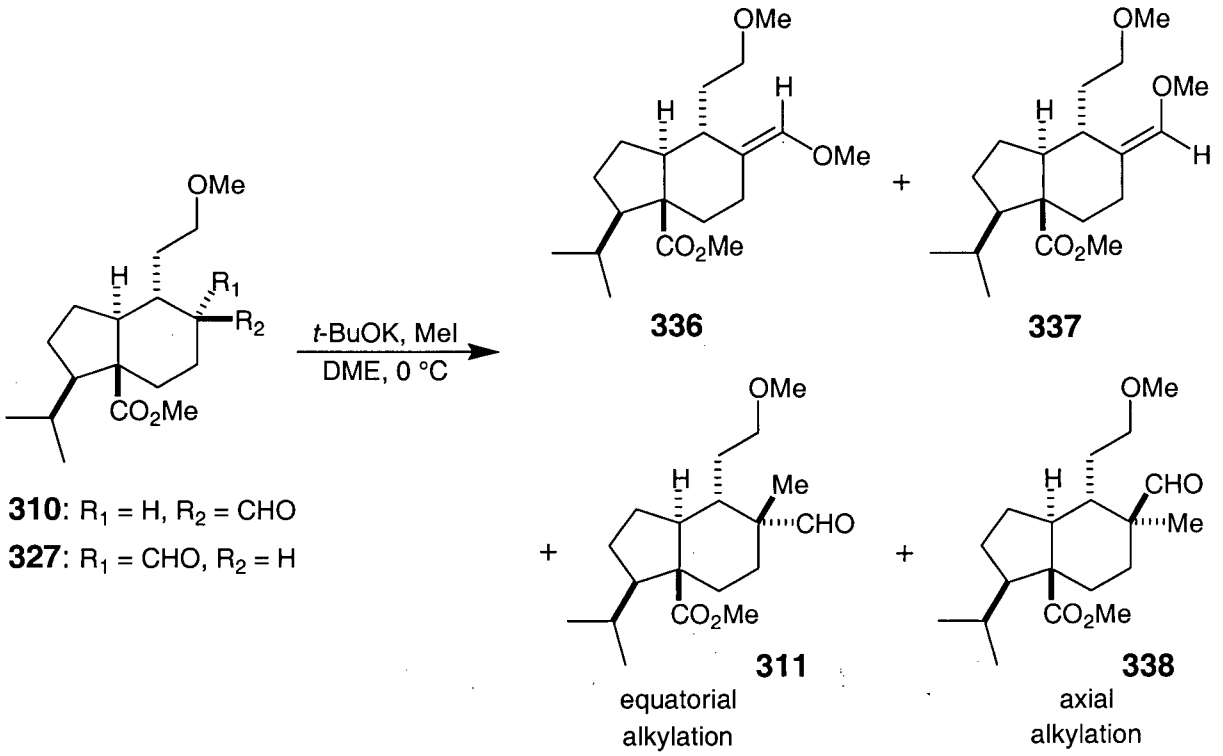
Scheme 3.70: Axial alkylation of aldehyde 331 as shown by Snider *et al.* in a total synthesis of (+)-erinacine[159]

Based on these and other results from the literature, it was expected that the alkylation of aldehydes **310** and **327** would provide the axial aldehyde, thereby establishing the correct relative configuration at the newly generated carbon chirality center. Indeed, examination of molecular models of the enolates derived from aldehydes **310** and **327** indicated that the two axial protons on the α-face of the molecule (H_A and H_B) should hinder the axial approach of the electrophile (see **335**, **Scheme 3.71**). The side chain on C-5, which resides in the equatorial position, was not expected to exert any influence on the approach of the electrophile. Thus, the axial aldehyde (**311**) was expected to be the major product from this alkylation reaction.



Scheme 3.71: Expected alkylation of aldehyde 310

Subjection of aldehydes **310** and **327** to the alkylation conditions reported by Ireland and Mander provided a mixture of products. ^{1}H NMR analysis of the crude product mixture revealed the presence of two methyl enol ethers and two new aldehydes (**Scheme 3.72**).

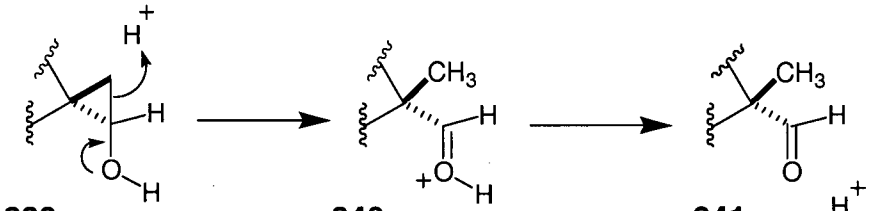


Scheme 3.72: Attempted alkylation of aldehydes 310 and 327 under the reaction conditions reported by Ireland and Mander

The mixture of products obtained from the alkylation reaction of aldehyde **310** proved inseparable by flash column chromatography on silica gel. The methyl enol ethers produced were evidenced by two singlets at δ = 5.68 and δ = 5.63 (60%, ratio 3.6:1) in the ^{1}H NMR spectrum of the mixture. The two new aldehydes gave rise to singlets at δ = 9.58 and δ = 9.24 (32%, ratio 7.4:1). The signal at δ = 9.58 was attributed to the desired product (**311**) based on the mechanistic arguments presented in the preceding discussion. The spectroscopic verification of the relative configuration of the newly generated carbon chirality center was carried out at a later stage on a material derived from aldehyde **311**.

Unfortunately, all attempts to alkylate aldehydes **310** and **327** under a variety of conditions were plagued by the generation of methyl enol ethers as the major products. Similarly, attempts to alkylate hydrazone and imine derivatives of aldehydes **310** and **327** were not successful.

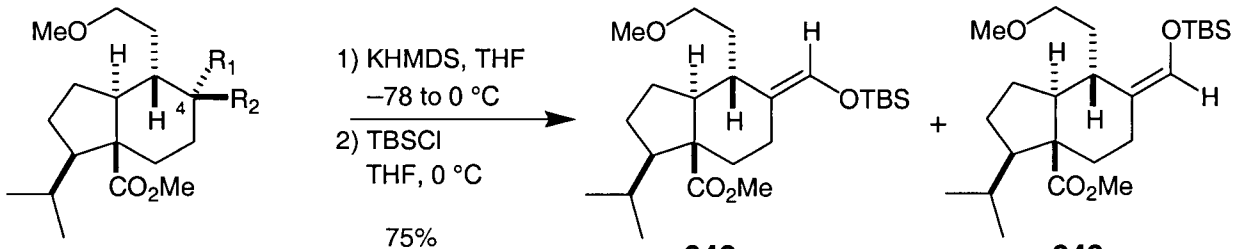
In view of these results, a four step sequence was used to install the methyl group at the C-4 position. This method relied on the known Brönsted acid catalyzed rearrangement of cyclopropanols to methyl aldehydes[160-165] (**Scheme 3.73**).



339 **340** **341**

Scheme 3.73: Brønsted acid catalyzed rearrangement of cycropropanols to α-methyl aldehydes

The first step in this alkylation sequence was the conversion of aldehydes **310** and **327** to a mixture of silyl enol ethers **342** and **343** (**Scheme 3.40**). These silyl enol ethers were easily separable by flash column chromatography on silica gel. Although these materials could be characterized independently of each other, no effort was made to ascertain the geometry about the double bond of the major product.



310: R_1 = H, R_2 = CHO
327: R_1 = CHO, R_2 = H

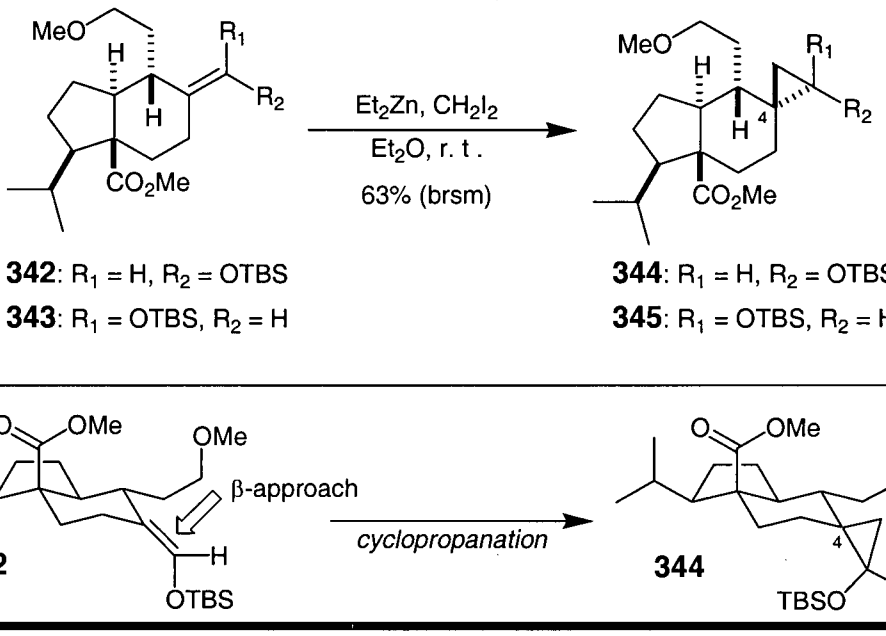
342 **343**

Scheme 3.74: Preparation of silyl enol ethers 342 and 343

The ^{1}H NMR spectrum of the major silyl enol ether displayed a one-proton singlet at $\delta = 6.00$ which was attributed to the alkenyl proton. The *tert*-butyldimethyl silyl group was evidenced by the appearance of a nine-proton singlet at $\delta = 0.88$ and two three proton singlets which coincided at $\delta = 0.07$. The ^{13}C NMR spectrum displayed two alkenyl carbon signals at $\delta = 121.6$ and $\delta = 132.7$. The IR spectrum of this material showed a carbonyl stretching absorption at 1724 cm^{-1} and an absorption at 1666 cm^{-1} which was attributed to the stretching of the carbon-carbon double bond. The molecular mass of the major silyl enol ether was confirmed by an HRMS measurement of its parent ion.

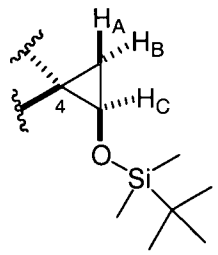
The ^{1}H NMR spectrum of the minor silyl enol ether showed a one-proton singlet at $\delta = 5.97$ which was attributed to the alkenyl proton. The *tert*-butyldimethyl silyl group was evidenced by the appearance of a nine-proton singlet at $\delta = 0.90$ and two three proton singlets which coincided at $\delta = 0.08$. The ^{13}C NMR spectrum displayed two alkenyl carbon signals at $\delta = 119.2$ and $\delta = 134.0$. No IR or mass spectral data was recorded on this material.

At this point a Simmons-Smith[166-168] reaction was utilized to prepare cyclopropanes **344** and **345** from the mixture of silyl enol ethers (**342** and **343**, **Scheme 3.75**). The resulting mixture of cyclopropanes proved inseparable by flash column chromatography on silica gel. Analysis of molecular models of compounds **342** and **343** indicated that the cyclopropanation reaction should occur predominantly from the β-face of the double bond (see inset, **Scheme 3.75**). Therefore, it was expected that the relative configuration of the carbon chirality center at C-4 of compounds **344** and **345** would be as shown.



Scheme 3.75: Simmons-Smith cyclopropanation of silyl enol ethers 342 and 343

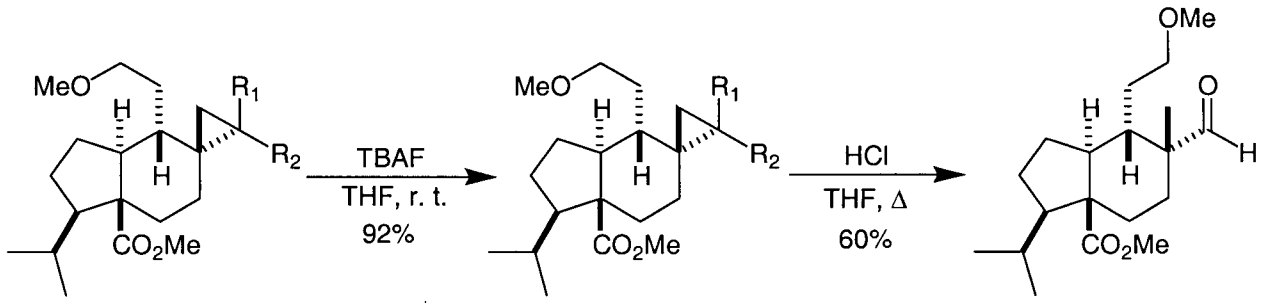
Although the mixture of cyclopropyl silyl ethers **344** and **345** was inseparable, the major product could be independently prepared form the major enol ether. The ^{1}H NMR spectrum of the major product of the cyclopropanation reaction showed clear evidence for the presence of the cyclopropane ring (see **Figure 3.31**). The ^{13}C NMR spectrum displayed the correct number of signals. A *J*-mod ^{13}C NMR experiment demonstrated the presence of seven methylene groups and a total of fourteen methyl and methine groups. The molecular mass of the major cyclopropyl silyl ether was verified through an HRMS measurement of its parent ion.



H_A: δ = 0.11-0.15 (dd, *J* = 6.2, 3.4 Hz)
H_B: δ = 0.63-0.80 (dd, *J* = 6.7, 6.2 Hz)
H_C: δ = 3.21-3.25 (dd, *J* = 6.7, 3.4 Hz)

Figure 3.31: Selected NMR data for the major cyclopropyl enol ether obtained from the Simmons-Smith reaction of enol ethers 342 and 343

The mixture of cyclopropyl enol ethers could be efficiently converted to the corresponding cyclopropanols (**346** and **347**) upon deprotection with TBAF (**Scheme 3.76**). The cyclopropanols were not characterized, but were immediately converted to aldehyde **311** by treatment with mineral acid in hot THF.



344: R_1 = H, R_2 = OTBS

345: R_1 = OTBS, R_2 = H

346: R_1 = H, R_2 = OH

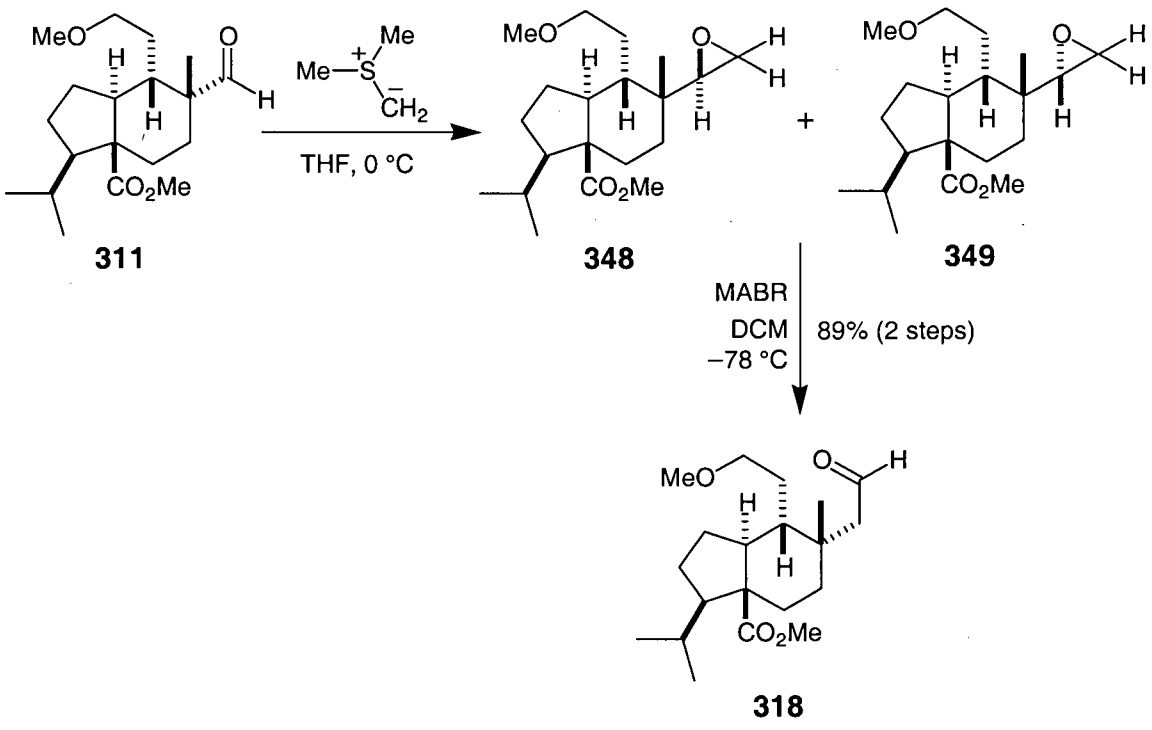
347: R_1 = OH, R_2 = H

311

Scheme 3.76: Preparation of aldehyde 311

The spectral data collected on aldehyde **311** was consistent with the assigned structure. The ^{1}H NMR spectrum contained the correct number of signals, including a one-proton singlet at δ = 9.58 which was attributed to the aldehyde group and a three-proton singlet at δ = 1.04 which accounted for the methyl group α to the aldehyde. Note that the ^{1}H NMR spectrum of the major α-methyl aldehyde obtained using the reaction conditions described by Ireland and Mander also displayed a singlet at δ = 9.58. The ^{13}C NMR spectrum displayed the correct number of signals, including a resonance at δ = 206.7 which was attributed to the aldehyde carbonyl carbon. A *J*-mod ^{13}C NMR spectrum demonstrated the presence of six methylene groups and a total of ten methyl and methine groups. The IR spectrum showed a carbonyl stretching absorption at 1721 cm^{-1}. Finally, the molecular mass was confirmed through an HRMS of the parent ion.

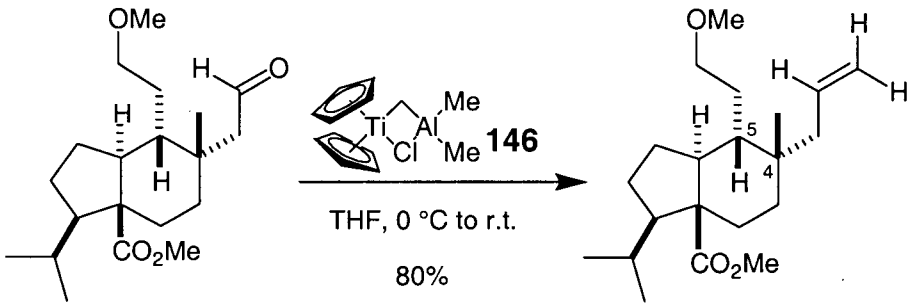
The homologation of aldehyde **311** to aldehyde **318** was efficiently accomplished using the same sequence of reactions used to prepare aldehyde **310** (**Scheme 3.77**). Thus, a mixture of epoxides **348** and **349** was prepared from aldehyde **311** using the Corey-Chaikovsky epoxidation protocol[153-156] (see **Scheme 3.68**). This mixture of epoxides converged to aldehyde **318** upon treatment with MABR[140] (see **Scheme 3.47**).



Scheme 3.77: Preparation of aldehyde 318

The IR spectrum of aldehyde **317** exhibited a carbonyl stretching absorption at 1720 cm^{-1}. The ^1H NMR spectrum contained the correct number of signals. The aldehyde proton resonated at $\delta = 9.81$ (dd, $J = 3.9, 2.7$ Hz). The ^{13}C NMR spectrum displayed the correct number of signals, including a resonance at $\delta = 204.0$ which was attributed to the aldehyde carbonyl carbon. A *J*-mod ^{13}C NMR spectrum demonstrated the presence of seven methylene groups and a total of ten methyl and methine groups.

The synthetic plan called for the conversion of aldehyde **318** to alkene **317**. The desired transformation could be achieved using a Wittig or Takai[82-84,87] olefination protocol. However, the best yield of alkene **317** was obtained using Tebbe's methylenation reagent[81] (**146**, **Scheme 3.78**).



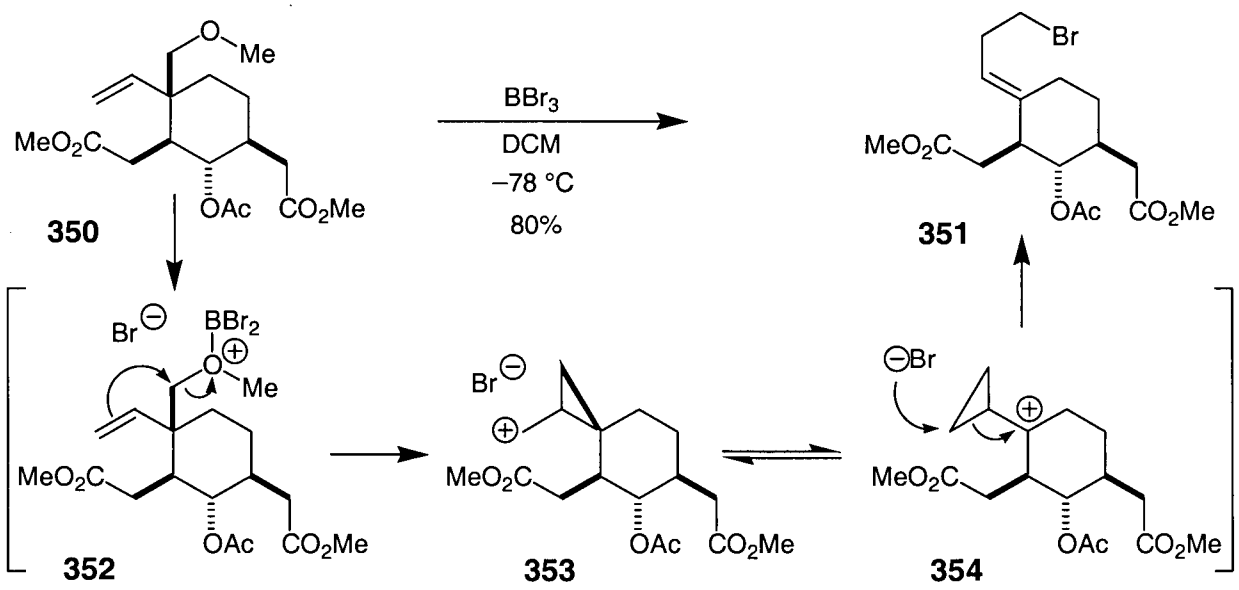
318 **317**

Scheme 3.78: Preparation of alkene 317

The ^{1}H NMR spectrum of alkene **317** displayed a one-proton multiplet at $\delta =$ 5.66-5.79 (dddd, $J =$ 17.0, 10.2, 8.0, 6.9 Hz) and a two-proton multiplet at $\delta =$ 4.92-5.02. These signals were attributed to the three olefinic protons in the molecule. The ^{13}C NMR spectrum displayed the correct number of signals, including two olefinic carbon resonances at $\delta =$ 116.9 and $\delta =$ 135.5. A *J*-mod ^{13}C NMR experiment showed clearly the presence of eight methylene groups and a total of ten methyl and methine groups. An HRMS of the parent ion confirmed the molecular mass of alkene **317**.

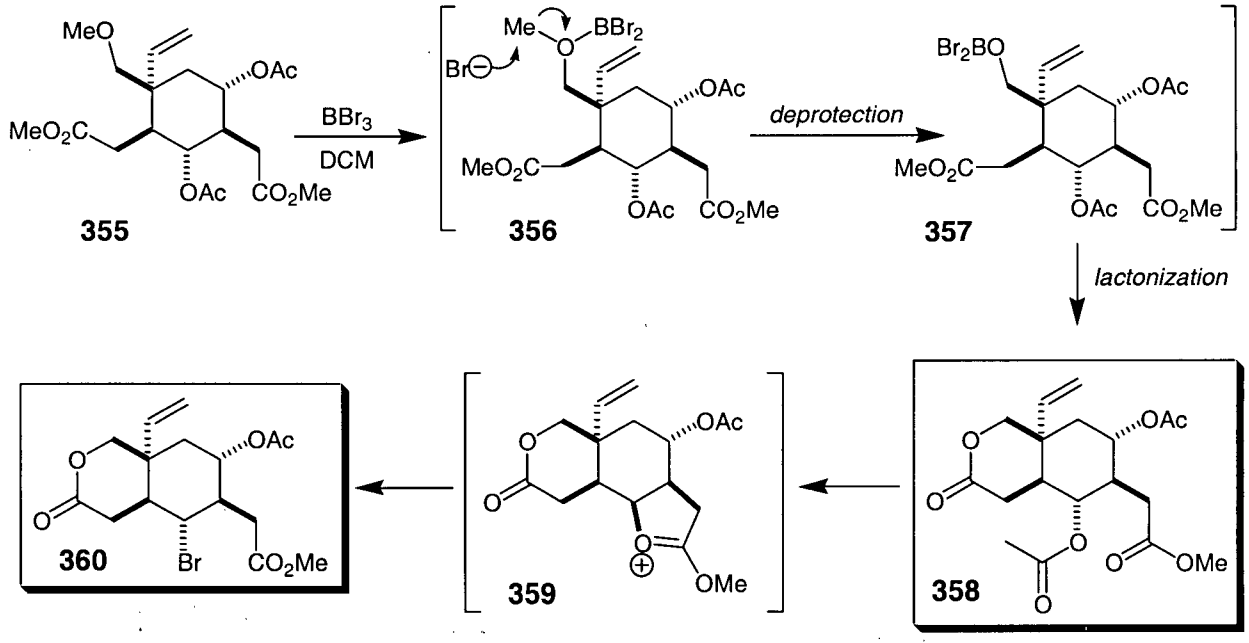
Having efficiently installed an allyl group at C-4, it became necessary to transform the 2-methoxy ethyl group at C-5 into an alkenyl chain that would participate in a ring-closing metathesis reaction to construct the seven-membered ring. This required the conversion of methyl ether **317** to the corresponding primary alcohol. This transformation is typically carried out using a Lewis acid, BBr_3 being the most widely used.

Grieco[148] has shown that the conditions used for the deprotection of methyl ethers of highly functionalized substrates can often result in the promotion of side reactions. For example, treatment of compound **350** with BBr_3 in DCM at low temperature provides homoallylic bromide **351** as the major product (**Scheme 3.79**). This reaction is thought to occur through the initial activation of the ether group by coordination of the ether oxygen atom to the Lewis acid, as shown in **352**. The vinyl group attacks the activated methylene group and forms a carbocationic species (see **353** and **354**). Nucleophilic attack of carbocation **354** by bromide results in the formation of the observed product.



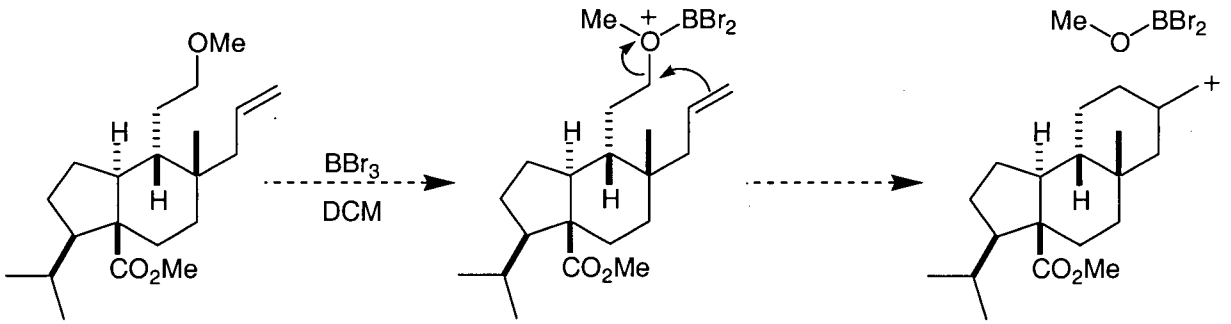
Scheme 3.79: Formation of homoallylic bromide 351 during the attempted deprotection of methyl ether 350 using BBr_3[148]

The attempted deprotection of a related substrate used in the same study led to the formation of a different side product[149] (**Scheme 3.80**). Treatment of **355** with BBr_3 in DCM resulted in the formation of two main products (**358** and **360**). Deprotection of the methyl ether proceeds as expected to generate a primary alkoxide bound to the Lewis acid (**357**). This material cyclizes onto the adjacent methyl ester to form lactone **358**, which was the desired product. Unfortunately, the Lewis acid also activates one of the acetate groups to form the stabilized oxonium ion **359**. Attack of **359** by bromide results in the formation of **360**.



Scheme 3.80: Formation of lactone 358 and bromide 356 during the BBr_3 mediated deprotection of methyl ether 360[149]

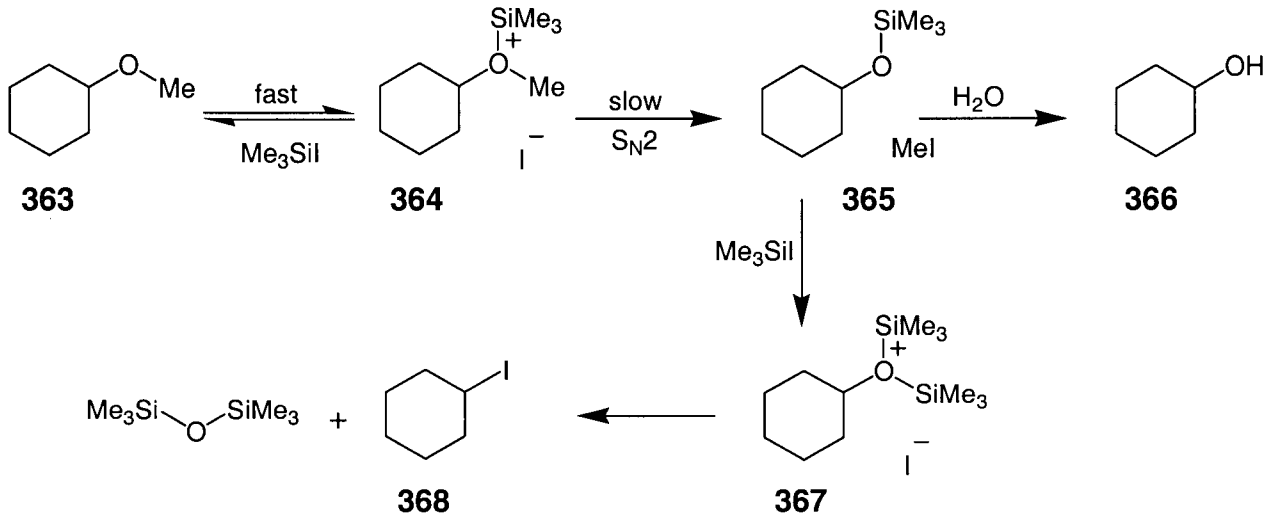
The relative scarcity of functional groups in methyl ether **317** indicated that the only possible side reaction would involve the attack of the alkene double bond onto the methylene group of the activated ether as shown in **361** (**Scheme 3.81**). Thus, in addition to the desired primary alcohol, side products arising from cation **362** were also expected.



317 **361** **362**

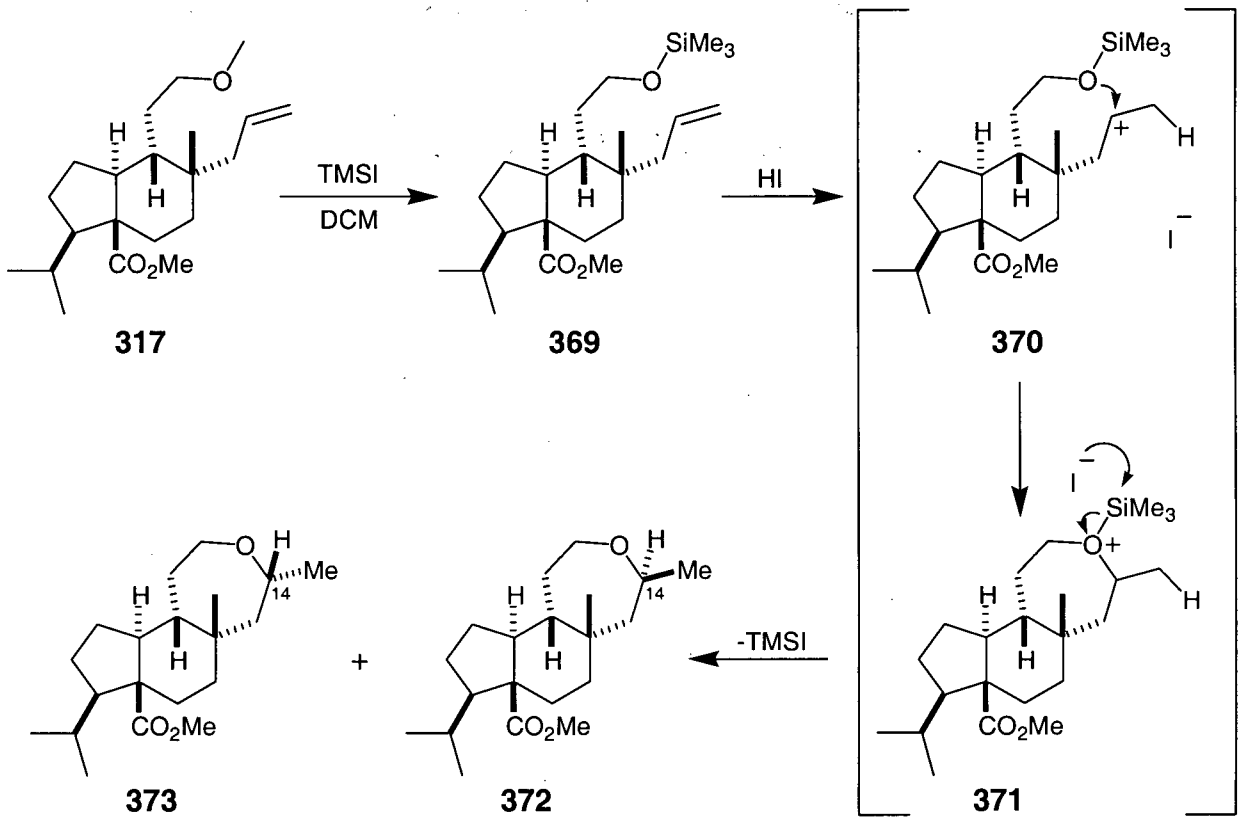
Scheme 3.81: Potential side reaction during the BBr_3 mediated deprotection of methyl ether 317

Remarkably, methyl ether **317** proved stable to the deprotection conditions described by Grieco, even after an extended period of time. As a result, the transformation of the methyl ether to a primary alcohol was attempted using TMSI as the Lewis acid. According to Jung,[150] the deprotection of methyl ethers with TMSI occurs as shown in **Scheme 3.82**. The methyl ether (**363**) and TMSI exist in a fast equilibrium with the activated ether (**364**). Presumably the conversion of the activated ether (**364**) to a trimethyl silyl ether (**365**) occurs through an S_N2 mechanism. The trimethyl silyl ether is converted to the corresponding alcohol (**366**) during an aqueous work-up. However, in the presence of excess TMSI the trimethyl silyl ether provides the corresponding alkyl iodide (**368**).



Scheme 3.82: Mechanism for the conversion of alkyl methyl ethers to alcohols and alkyl iodides as proposed by Jung[150]

Unfortunately, treatment of alkene **317** with a large excess of TMSI (~ 10 equiv.) did not provide either the primary alcohol or the corresponding alkyl iodide (**Scheme 3.83**). Analysis of the ^{1}H NMR spectrum of the crude product mixture indicated that the two major products were cyclic ethers **372** and **373**, which are epimeric at C-14 (mulinane numbering).

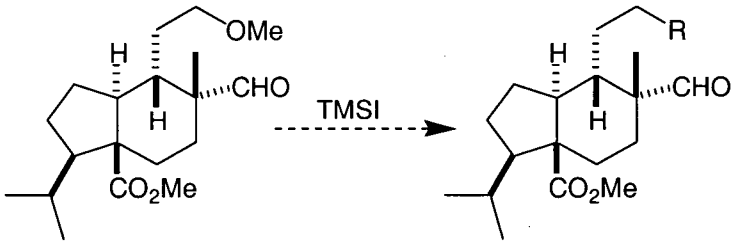


Scheme 3.83: Attempted deprotection of methyl ether 317 with an excess of TMSI

It is likely that the formation of ethers **372** and **373** occurred through the intermediacy of the desired trimethyl silyl ether **369**. The double bond of **369** may react with adventitious HI to generate a secondary carbocation (**370**). The juxtaposition of the trimethyl silyl ether and the secondary carbocation facilitates the formation of the oxonium ion **371**. This material provides the observed ethers upon elimination of TMSI.

The ^{1}H NMR spectrum of the major ether showed three one-proton multiplets at δ = 3.44-3.48, δ = 3.63-3.68 and δ = 4.20-2.26, which account for all the protons adjacent to the ether oxygen atom. A three-proton doublet at δ = 1.95 (J = 6.8 Hz) was attributed to the methyl group α to the ether oxygen atom. The ^{13}C NMR spectrum displayed the correct number of signals. A *J*-mod ^{13}C NMR experiment demonstrated the presence of seven methylene groups and a total of ten methyl and methine groups. The relative configuration of the carbon chirality center at C-14 (mulinane numbering) was not determined.

Due to the failure to deprotect methyl ether **317**, it was decided to revise the synthetic strategy. According to the mechanistic rationale presented by Jung,[150] the TMSI mediated deprotection of methyl ether **311** should provide either alcohol **374** or alkyl iodide **375** (**Scheme 3.84**).



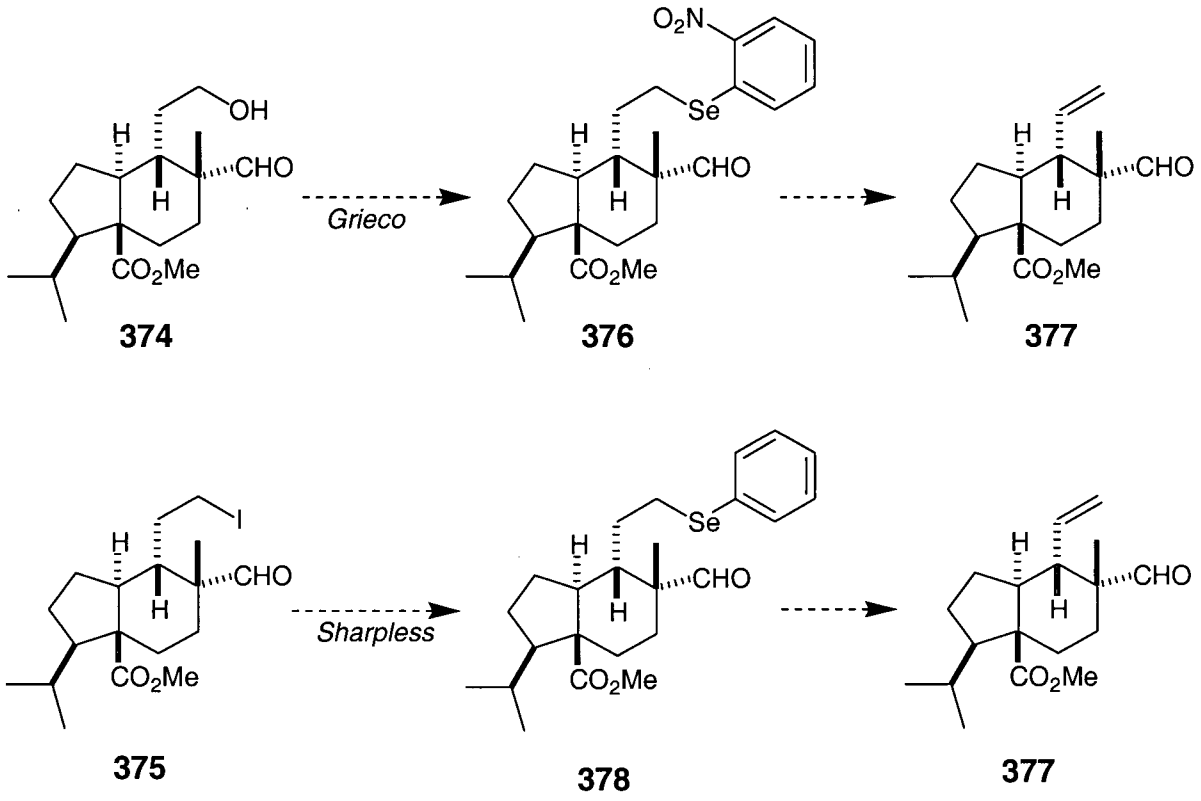
311

374 : R = OH

375 : R = I

Scheme 3.84: Proposed conversion of methyl ether 311 to alcohol 374 or alkyl iodide 375

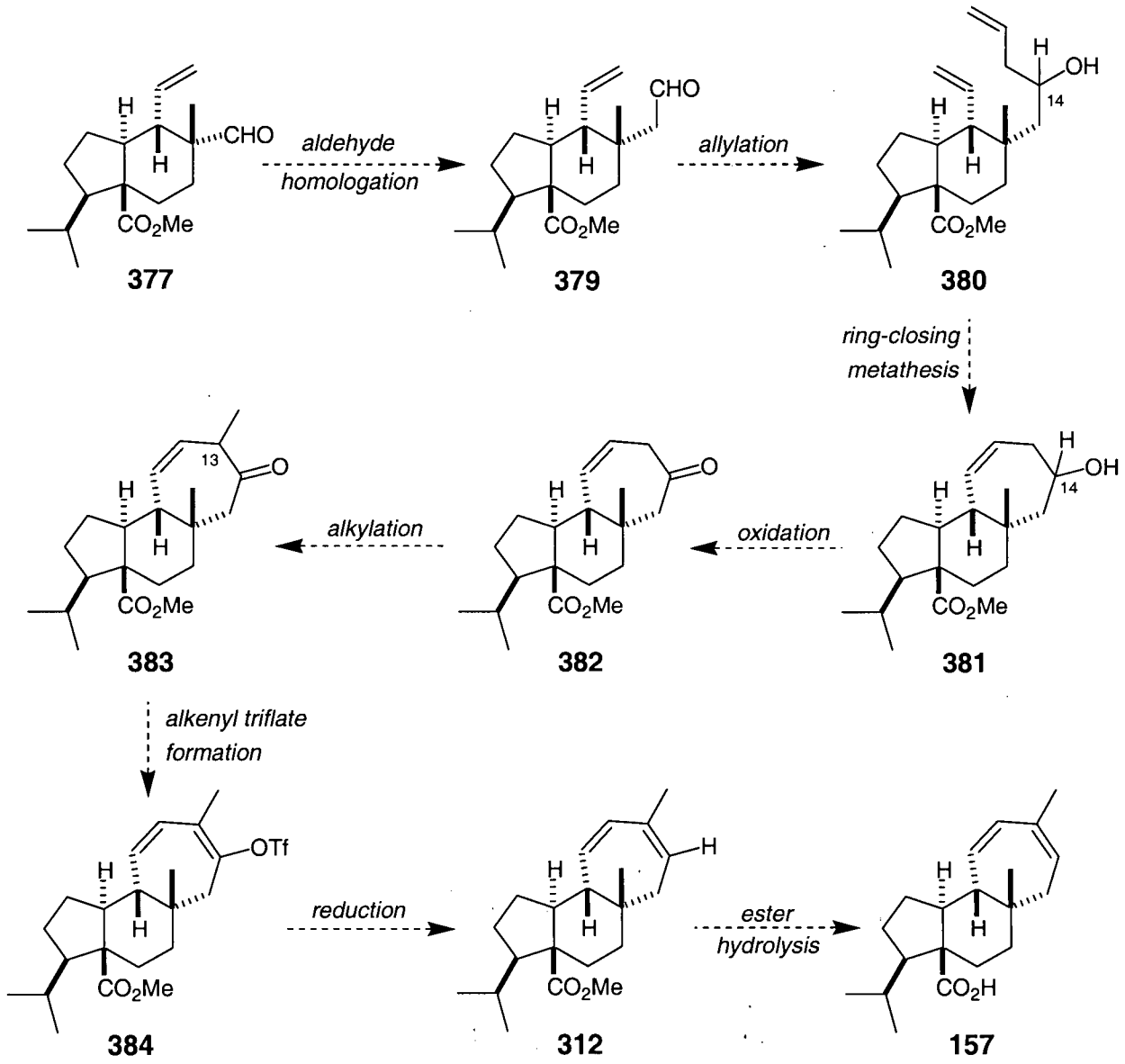
It was recognized that primary alcohol **374** could potentially be converted to the corresponding *ortho*-nitrophenyl selenide (**376**) using the procedure developed by Grieco[169] (**Scheme 3.85**). This material, in turn, should furnish alkene **377** upon oxidation of the selenide and subsequent *syn*-elimination.[170] Alternatively, alkyl iodide **375** could be converted to the corresponding phenyl selenide (**378**) as described by Sharpless.[108,171] Again, oxidation of the selenide and subsequent *syn*-elimination of the corresponding selenoxide should provide alkene **377**.



Scheme 3.85: Two possible preparations of alkene 377

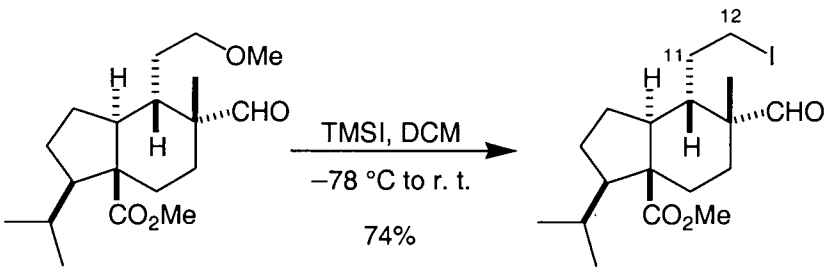
If the preparation of alkene **377** proved successful, this material could potentially yield access to the mulinane family of natural products using the sequence of reactions outlined in **Scheme 3.86**. Thus, homologation of aldehyde **377** could be carried out as before (see **Scheme 3.77**). Allylic alcohol **380** should be accessible by treatment of aldehyde **379** with allyl magnesium bromide. The relative configuration of the carbon chirality center at C-14 (mulinane numbering) does not need to be defined at any stage. Subjection of diene **380** to ring-closing metathesis conditions should provide the desired tricyclic system (**381**). Oxidation of the secondary alcohol under neutral conditions should provide the corresponding β,γ-unsaturated enone (**382**). Alkylation of enone **377** with methyl iodide would install the requisite methyl group at C-13 (mulinane numbering). Note that compound **383** possesses the complete carbocyclic framework present in the mulinane family of natural products. Formation of alkenyl triflate **384** was expected to occur by treatment of the thermodynamic enolate of enone **383** with a suitable triflating agent. Reduction of the triflate group was expected to provide the

desired seven-membered ring diene. Finally, hydrolysis of the methyl ester on **312** would provide (±)-mulin-11,13-dien-20-oic acid **157**.



Scheme 3.86: Revised synthetic route to (±)-mulin-11,13-dien-20-oic acid 157

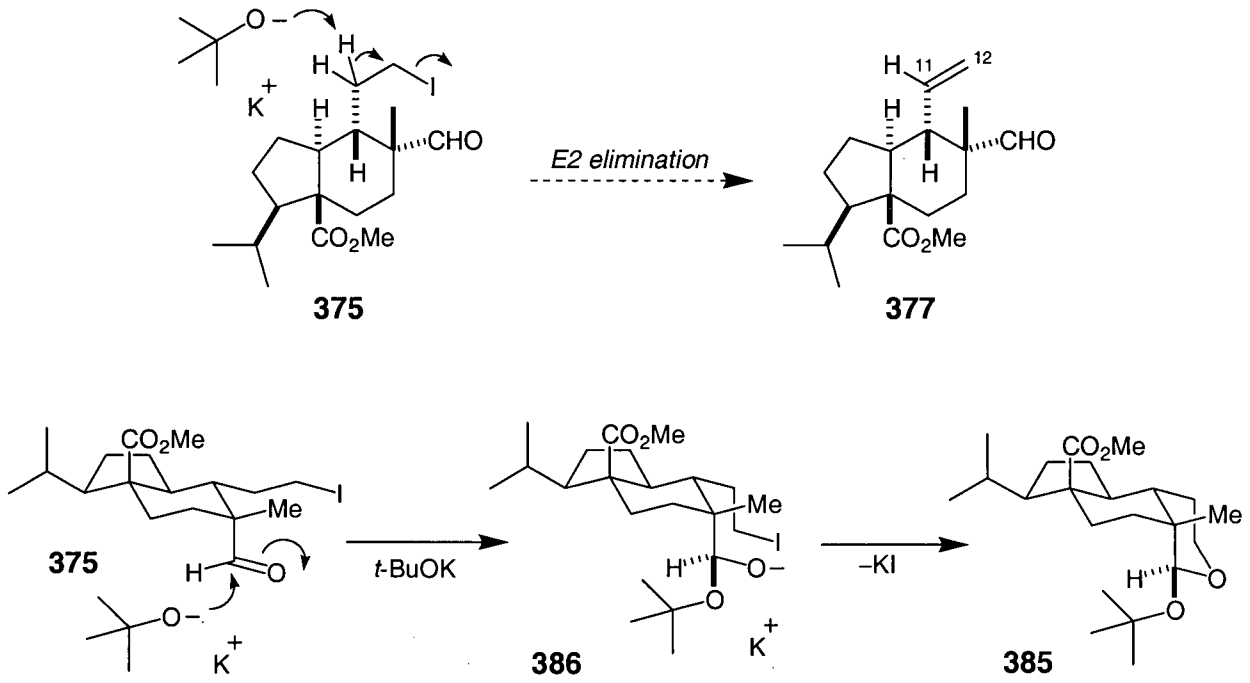
Treatment of aldehyde **311** with TMSI provided alkyl iodide **375** as the major product (**Scheme 3.87**). The methylene protons at C-12 (mulinane numbering) of iodide **375** resonated at δ = 3.04-3.15 (ddd; J = 9.5, 9.5, 9.5 Hz) and δ = 3.29-3.37 (ddd; J = 9.5, 9.5, 4.9 Hz) in the ^{1}H NMR spectrum. The aldehyde proton gave rise to a signal at δ = 9.48.



311 **375**

Scheme 3.87: Preparation of iodide 375

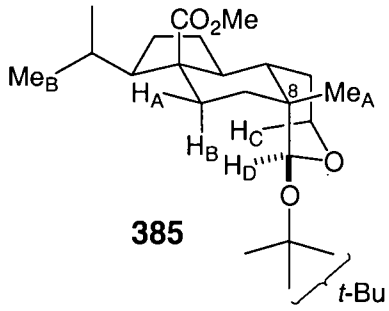
At this time it was postulated that treatment of iodide **375** with a bulky base would promote the E2 elimination of HI to establish a double bond between C-11 and C-12 (mulinane numbering). However, treatment of iodide **375** with *t*-BuOK resulted in the formation of mixed acetal **385**. Presumably, the approach of *t*-butoxide anion to the hydrogen atoms β to the iodine atom is too sterically encumbered to allow for the E2 elimination process to occur. The formation of acetal **385** is thought to occur as shown in **Scheme 3.88**. Thus, 1,2 addition of the *t*-butoxide anion to the aldehyde generates anion **386**. This material may revert back to aldehyde **375** and the *t*-butoxide anion. Alternatively, anion **386** may undergo an irreversible internal S_N2 displacement reaction to generate the observed mixed acetal.



Scheme 3.88: Attempted E2 elimination of HI from alkyl iodide 375, preparation of mixed acetal 385

The ^{1}H NMR spectrum of acetal **385** displayed a nine-proton singlet at $\delta = 1.19$ which was attributed to the *t*-butyl group. The acetal proton gave rise to a singlet at $\delta = 4.80$. The protons on the methylene group adjacent to the acetal oxygen atom were observed as one-proton multiplets at $\delta = 3.70\text{-}3.77$ and $\delta = 3.52\text{-}3.65$. The ^{13}C NMR spectrum displayed the correct number of signals, including a resonance at $\delta = 94.9$ which was attributed to the acetal carbon. The *t*-butyl group gave rise to a three-carbon resonance at $\delta = 28.8$. A *J*-mod ^{13}C NMR experiment demonstrated the presence of six methylene groups and a total of twelve methyl and methine groups. The molecular mass of this compound was verified through an HRMS measurement of its parent ion.

The relative configuration of the acetal carbon chirality center was determined using a number of 1D NOE difference experiments (**Figure 3.32**). Note that although acetal **385** is not useful in a synthetic sense, it served to confirm the conclusions regarding the relative configuration of the carbon chirality center at C-8 (mulinane numbering).



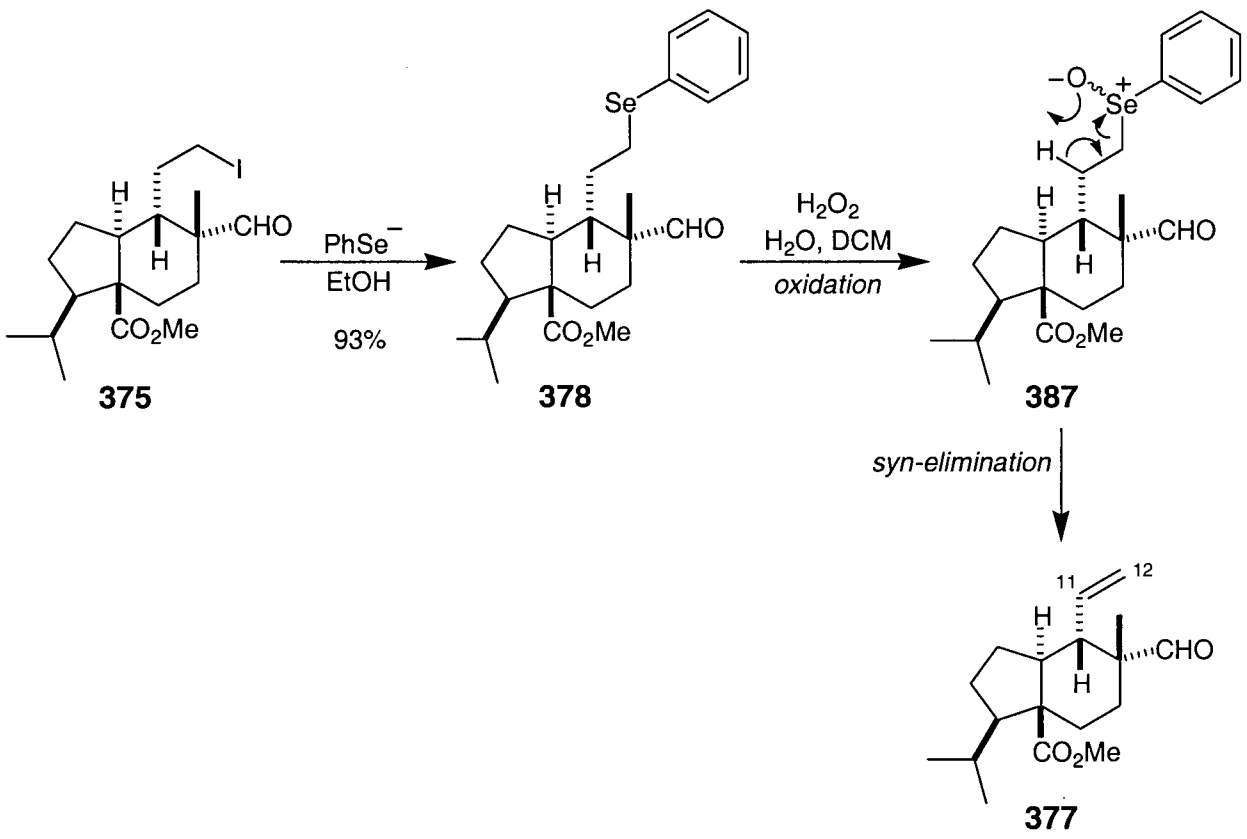
385

H_A: δ = 2.38-2.45 (ddd; *J* = 13.0, 3.6, 3.6 Hz)
H_B: δ = part of a multiplet at 1.07-1.34
H_C: δ = 3.52-3.65 (m)
H_D: δ = 4.80 (s)
Me_A: δ = 0.94 (s)
Me_B: δ = 1.00 (d; *J* = 6.4 Hz))
t-Bu : δ = 1.19 (s)

irradiation of H_D enhances H_B, H_C and *t*-Bu
irradiation of H_A enhances H_B and Me_B

Figure 3.32: Selected NOE difference data for acetal 385

In order to establish the double bond between C-11 and C-12 (mulinane numbering), iodide **375** was transformed into selenide **378** using the procedure outlined by Sharpless and Lauer.[108] (**Scheme 3.89**). The ^{1}H NMR spectrum of selenide **378** contained the correct number of signals. The phenyl group was evidenced by a three-proton multiplet at δ = 7.18-7.26 and a two-proton multiplet at δ = 7.42-7.48. The aldehyde proton gave rise to a singlet at δ = 9.51. The methylene group adjacent to the selenium atom was observed as a pair of multiplets at δ = 2.75-2.85 and δ = 3.03-3.12 with a mutual coupling constant of 11.9 Hz. The ^{13}C NMR spectrum displayed a two-carbon resonance at δ = 129.0, a two-carbon resonance at 132.6 and two one-carbon resonances at δ = 126.8 and δ = 130.1, all of which were assigned to the phenyl group. A *J*-mod ^{13}C NMR experiment demonstrated the presence of six methylene groups and a total of fourteen methyl and methine groups. The molecular mass selenide **378** was confirmed through an HRMS measurement of its parent ion.

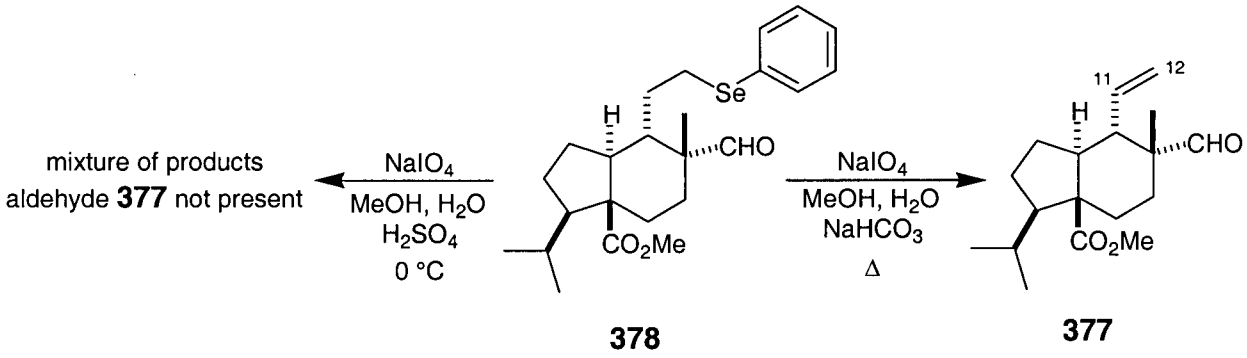


Scheme 3.89: Preparation of selenide 378 and alkene 377

The oxidation of selenide **378** to the corresponding selenoxide, and the subsequent *syn*-elimination reaction (see **387**, **Scheme 3.89**) that was to establish the double bond between C-11 and C-12 (mulinane numbering) of alkene **377** was not a straightforward process. Treatment of selenide **378** with hydrogen peroxide provided a mixture of products. Alkene **377** could be isolated from this mixture in low yield.

The three alkenyl protons of compound **377** gave rise to a one-proton multiplet at δ = 5.72-5.84 and a two-proton multiplet at δ = 5.05-5.12 in the ^{1}H NMR spectrum. The aldehyde proton was observed as a singlet at δ = 9.56. The ^{13}C NMR spectrum of alkene **377** displayed a resonance at δ = 118.0 and a resonance at δ = 136.2, which were both attributed to the alkenyl group.

The low yield of alkene **377** prompted the exploration of alternative conditions for the oxidation of selenide **378**. The attempted oxidation of the phenyl selenide moiety of compound **378** with $NaIO_4$ in basic MeOH did provide the desired alkene, but in low yield. Alternatively, the oxidation of **378** with $NaIO_4$ under acidic conditions did not provide the desired alkene. Although the products from this reaction were not isolated, analysis of the ^1H NMR spectrum of the crude reaction mixture revealed that none of the products in the mixture possessed an aldehyde group.



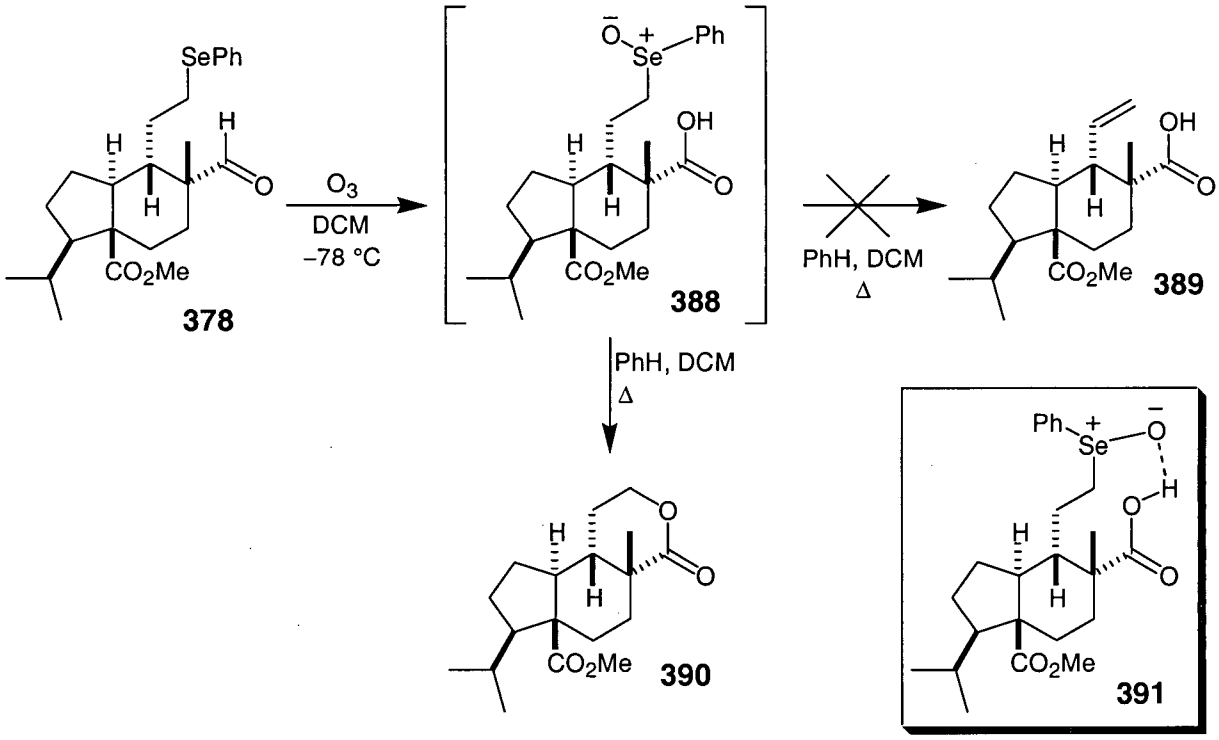
Scheme 3.90: Oxidation of Selenide 378 with $NaIO_4$

Clearly, the standard reagents for oxidation of selenides to selenoxides (H_2O_2, $NaIO_4$) were not sufficiently selective in the preparation of alkene **377**. At this stage, the identity of the side-products arising from the oxidation of **378** with H_2O_2 and $NaIO_4$ was unclear. However, it was hoped that a more selective oxidation protocol would provide clean access to alkene **377**. It has been shown that selenides are cleanly and quantitatively oxidized to selenoxides with ozone.[68] Indeed, this is the best method for the formation of selenoxides when special conditions are required for the elimination step.

Treatment of selenide **378** with ozone at –78 °C in DCM, followed by the addition of benzene and heating of the reaction mixture to reflux resulted in the clean formation of lactone **390** (**Scheme 3.91**). The ^1H NMR spectrum of lactone **390** exhibited the correct number of signals, including a two-proton multiplet at δ = 4.32-4.43 which was attributed to the methylene group adjacent to the lactone oxygen. The ^{13}C NMR spectrum displayed two carbonyl carbon resonances at δ = 176.2 and δ =

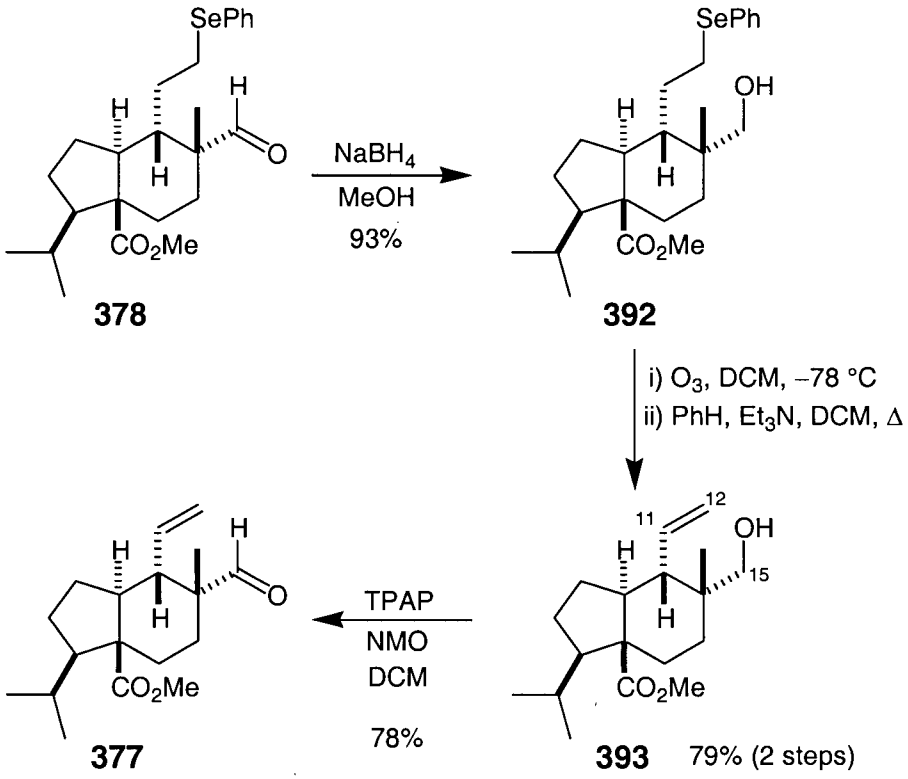
174.5. A resonance at $\delta = 66.9$ was attributed to the methylene group adjacent to the lactone oxygen. A *J*-mod ^{13}C NMR spectrum demonstrated the presence of six methylene groups and a total of eight methyl and methine groups.

The generation of lactone **390** likely occurs through the oxidation of the phenyl selenide moiety to the corresponding selenoxide and the oxidation of the aldehyde group to the corresponding acid. Reich *et al.*[172] have shown that the *syn*-elimination of selenoxides is suppressed in the presence of protic solvents as a result of the strong hydrogen bonding properties of selenoxides. It is possible that the carboxylic acid and the selenoxide functions of compound **388** form an intramolecular hydrogen bond (as in **391**), which helps to suppress the *syn*-elimination pathway to alkene **389**. As a result, the selenoxide decomposes through an alternate pathway.



Scheme 3.91: Oxidation of selenide 378 with ozone, formation of lactone 390

Due to the unexpected oxidation of the aldehyde group of compound **378** the oxidation of the selenide moiety was carried out on the corresponding alcohol. The reduction of aldehyde **378** to alcohol **392** was accomplished with the use of $NaBH_4$ in MeOH. It seemed likely that the hydroxyl group could also be involved in some form of internal hydrogen bonding thereby suppressing the *syn*-elimination of the selenoxide. Thus, it was postulated that the inclusion of an amine base in the reaction mixture during the elimination step would allow the clean *syn*-elimination of the selenoxide.[172]



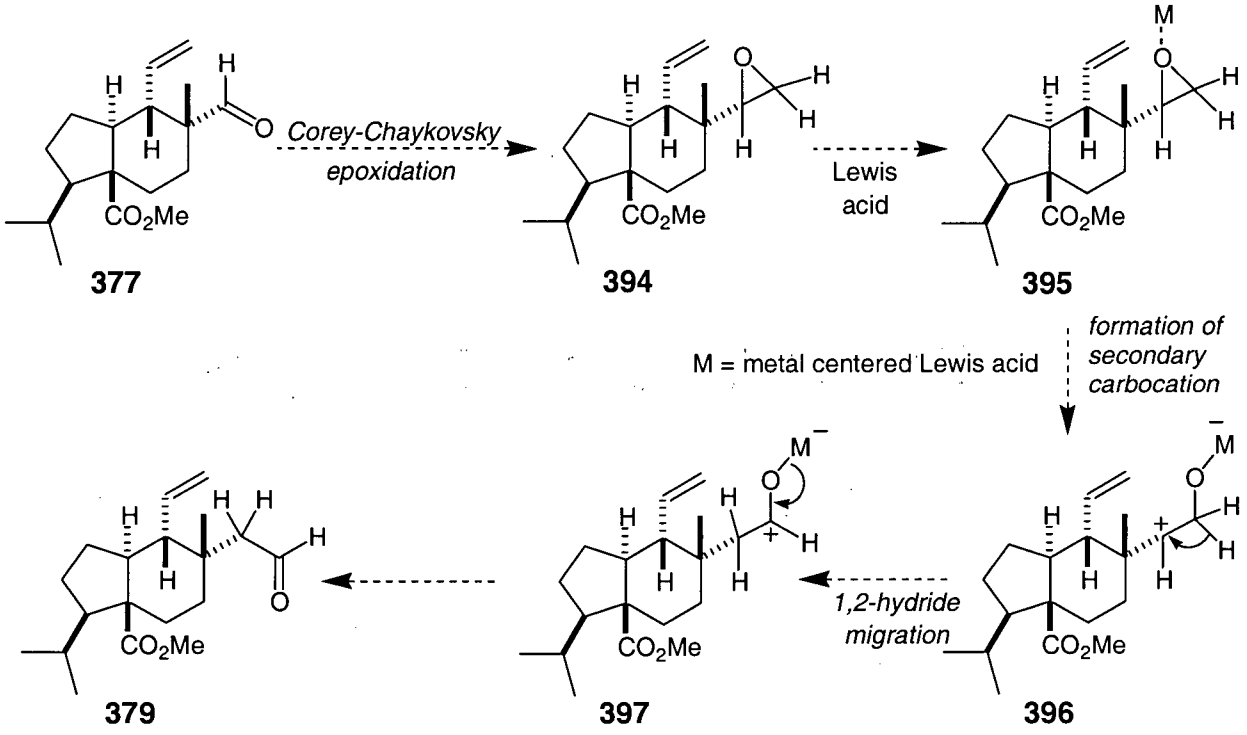
378 **392** **377** **393** 79% (2 steps)

Scheme 3.92: Preparation of alkenes 393 and 377

The oxidation of the phenyl selenide moiety of compound **392** was carried out with ozone at –78 °C. Benzene and triethyl amine were added to the solution of the selenoxide and the resulting mixture was heated to reflux. Gratifyingly, these reaction conditions provided efficient access to alkene **393**. Oxidation of the alcohol moiety of compound **393** using Ley's method provided aldehyde **377**, which had been previously characterized.

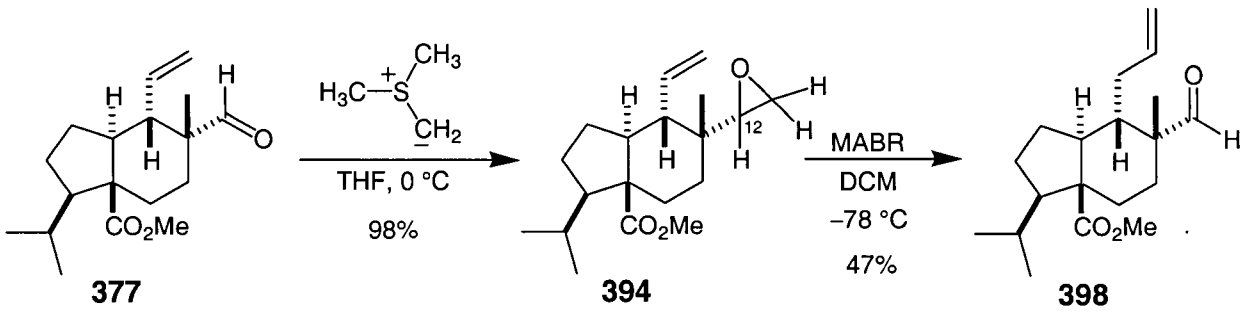
The ^{1}H NMR spectrum of alkene **393** exhibited a one-proton resonance at δ = 5.42-5.56 (ddd, J = 17.0, 10.0, 10.0 Hz) which was attributed to the alkenyl proton on C-11 (mulinane numbering). The alkenyl protons on C-12 (mulinane numbering) were observed as a one-proton multiplet at δ = 5.00-5.05 and a one-proton multiplet at δ = 4.97-5.00. The two carbinol protons at C-15 (mulinane numbering) were observed as a pair of doublets at δ = 3.68 and δ = 3.49 with a mutual coupling constant of 10.8 Hz. The ^{13}C NMR spectrum displayed the correct number of signals, including two alkenyl carbon resonances at δ = 137.4 and δ = 116.7. The carbinol carbon was observed at δ = 58.1. A *J*-mod ^{13}C NMR spectrum demonstrated the presence of six methylene groups and a total of nine methyl and methine groups.

The synthetic plan called for the homologation of aldehyde **377** to aldehyde **379**. This process was expected to occur through the formation of epoxides **394** from aldehyde **377** using the method developed by Corey and Chaykovsky (**Scheme 3.93**). Treatment of these epoxides with a Lewis acid should promote their rearrangement to the desired aldehyde. This rearrangement was expected to occur through the formation of secondary carbocation **396** followed by the migration of a hydride to form carbocation **397**. Intermediate **397** should give rise to the desired aldehyde. Note that this two-step aldehyde homologation sequence provided efficient access to aldehyde **318** from aldehyde **311** (see **Scheme 3.77**).



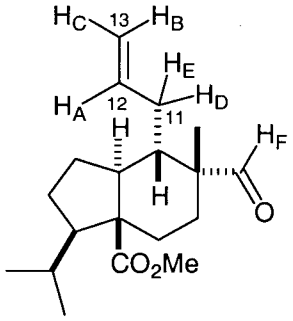
Scheme 3.93: Proposed homologation of aldehyde 377 to aldehyde 379

Subjection of aldehyde **377** to epoxidation conditions furnished a mixture of oxiranes (**394**), which are epimeric at C-12 (mulinane numbering, **Scheme 3.94**). This mixture of epoxides proved inseparable by flash column chromatography on silica gel. Treatment of epoxides **394** with a bulky Lewis acid (MABR, see **Scheme 3.47**) resulted in the formation of an aldehyde as the main product. Unfortunately, the spectral data collected on the acquired material indicated that it was not the desired product.



Scheme 3.94: Preparation of aldehyde 398.

The IR spectrum of aldehyde **398** displayed a carbonyl stretching absorption at 1719 cm^{-1}. The aldehyde proton was observed as a singlet at $\delta = 9.70$ in the ^1H NMR spectrum. Furthermore, the alkenyl protons at C-13 (mulinane numbering) were observed as a pair of signals at $\delta = 4.91$-4.96 and $\delta = 4.96$-5.02. The alkenyl proton at C-12 (mulinane numbering) resonated at $\delta = 5.74$-5.87. (see **Figure 3.33**). The ^{13}C NMR spectrum of alkene **398** displayed the correct number of signals, including a carbonyl carbon resonance at $\delta = 207.0$. In addition, the alkenyl carbons gave rise to signals at $\delta = 139.1$ and $\delta = 115.4$.



398

H_A: $\delta = 5.74$-5.87 (dddd)
$J_{AB} = 17.0$ Hz
$J_{AC} = 10.1$ Hz
$J_{AD} = J_{AE} = 7.0$ Hz

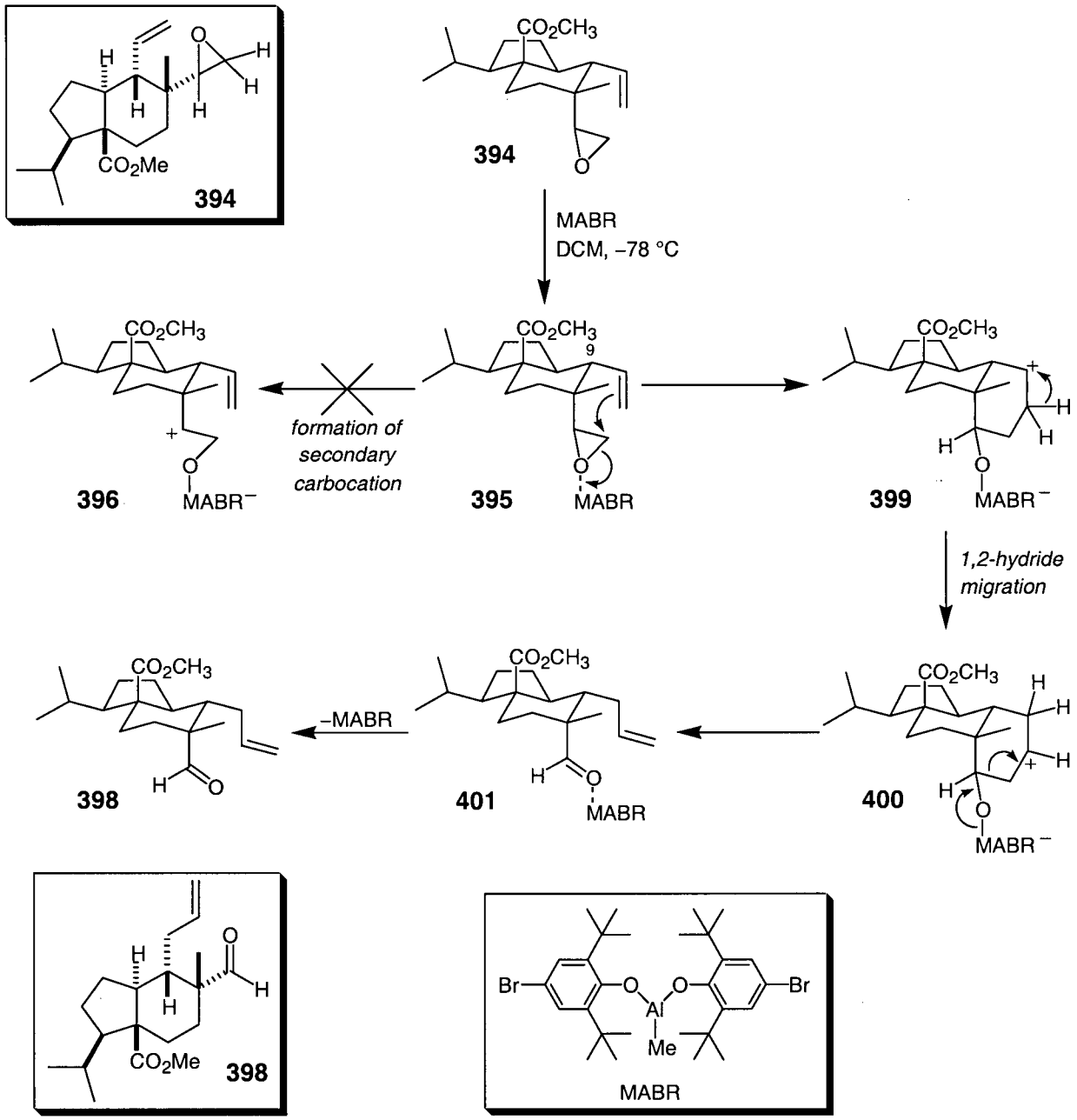
H_B: $\delta = 4.96$-5.02 (ddd)
$J_{AB} = 17.0$ Hz
$J_{BC} = 3.0$ Hz
J_{BD} or $J_{BE} = 1.7$ Hz

H_C: $\delta = 4.91$-4.96 (ddd)
$J_{AC} = 10.1$ Hz
$J_{BC} = 3.0$ Hz
J_{CD} or $J_{CE} = 1.5$ Hz

H_F: $\delta = 9.70$ (s)

Figure 3.33: Selected ^1H NMR data for alkene 398

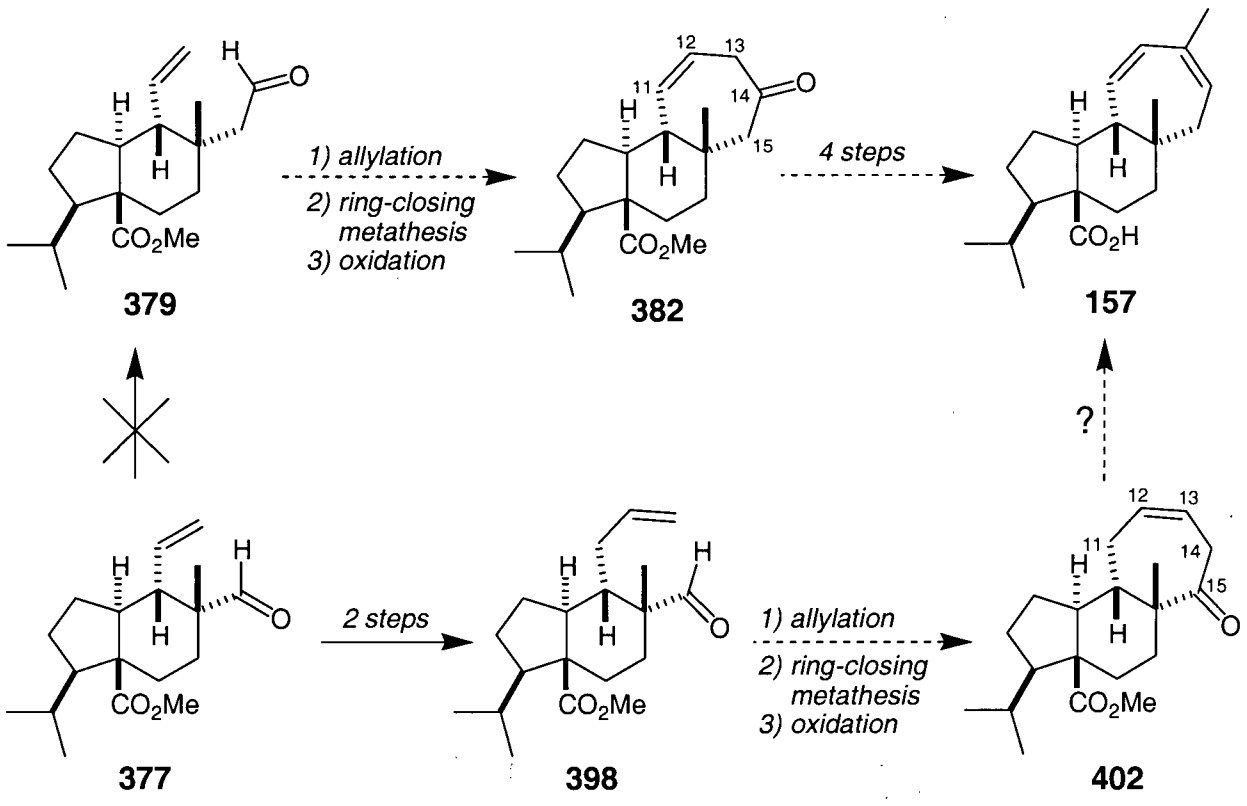
A proposed mechanism for the unexpected formation of alkene **398** is presented in **Scheme 3.95**. The first step involves the coordination of the oxirane oxygen of compound **394** to the Lewis acid to form complex **395**. It was expected that the Lewis acid would promote the formation of secondary carbocation **396**, which should give rise to the desired aldehyde (see **Scheme 3.93**). Instead, the activated epoxide is attacked by the vinyl group at C-9 (mulinane numbering). This results in the simultaneous opening of the epoxide ring and the formation of a carbon-carbon bond to provide secondary carbocation **399**. A 1,2-hydride shift leads from secondary carbocation **399** to secondary carbocation **400**. This material collapses to the Lewis acid bound aldehyde as shown (**400** to **401**). Finally, release of the catalyst provides the observed product (**398**).



Scheme 3.95: Proposed mechanism for the Lewis acid catalyzed formation of alkene 398 from epoxides 394

Recall that the synthetic plan called for the preparation of tricyclic enone **382** from aldehyde **379** using a three-step sequence (see **Scheme 3.86** and **Scheme 3.96**). Tricycle **382** has in place one of the double bonds present in mulin-11,13-dien-20-oic acid (**157**). In addition, the ketone carbonyl positioned at C-14 of compound **382** was expected to facilitate the installation of the methyl group at C-13 and the formation of a double bond between C-13 and C-14.

Unfortunately, all of bicyclic aldehyde **377** had been committed to forming aldehyde **398**. The implementation of the planned three-step sequence for the construction of the seven-membered ring using aldehyde **398** would furnish enone **402**. Despite the functional groups present on the seven-membered ring of enone **402**, its elaboration to compound **157** was not expected to be a straightforward process.

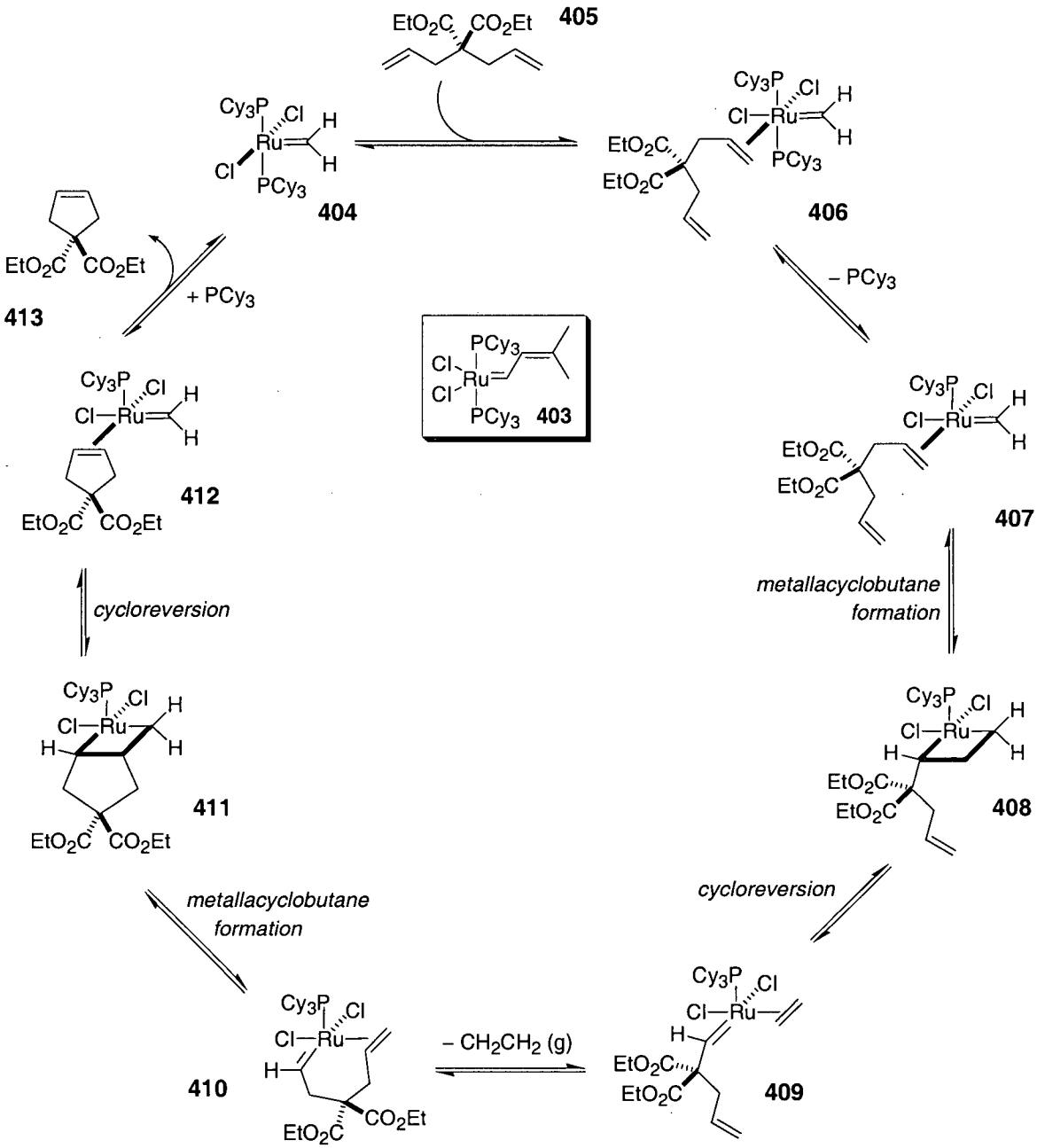


Scheme 3.96: Proposed construction of tricycle 402

The ring-closing diene metathesis reaction was viewed as a key step in the construction of the seven-membered ring of the mulinane diterpenoids. In recent years, this transformation has surfaced as one of the most powerful methods for ring construction.[173-176] A variety of catalysts for ring-closing metathesis exist. In this synthetic study, the ruthenium carbene catalyst **403** was utilized[177] (see **Scheme 3.97**). A kinetic study has revealed that the ring-closing metathesis reaction catalyzed by compound **404**, which is similar to catalyst **403**, occurs through two distinct pathways.[178]

In the case studied, the major catalytic cycle (>95%) is as depicted in **Scheme 3.97**. The first step involves coordination of one of the double bonds of diene **405** to the metal center of catalyst **404** to form complex **406**. Dissociation of a tricyclohexyl phosphine ligand results in the formation of complex **407**. An intramolecular metallacyclobutane formation reaction occurs to yield **408**. This complex can undergo a cycloreversion reaction to provide complex **409**, in which ethylene is coordinated to the metal center. The loss of ethylene gas leaves a vacant coordination site on the metal center. This site may be occupied by the second double bond of diene **405** to form complex **410**. A second intramolecular metallacyclobutane formation reaction ensues to provide **411**. A second cycloreversion reaction serves to close the carbocycle and yields complex **412**. Dissociation of the carbocycle from the metal center and the incorporation of a tricyclohexyl phosphine ligand regenerates the catalyst.

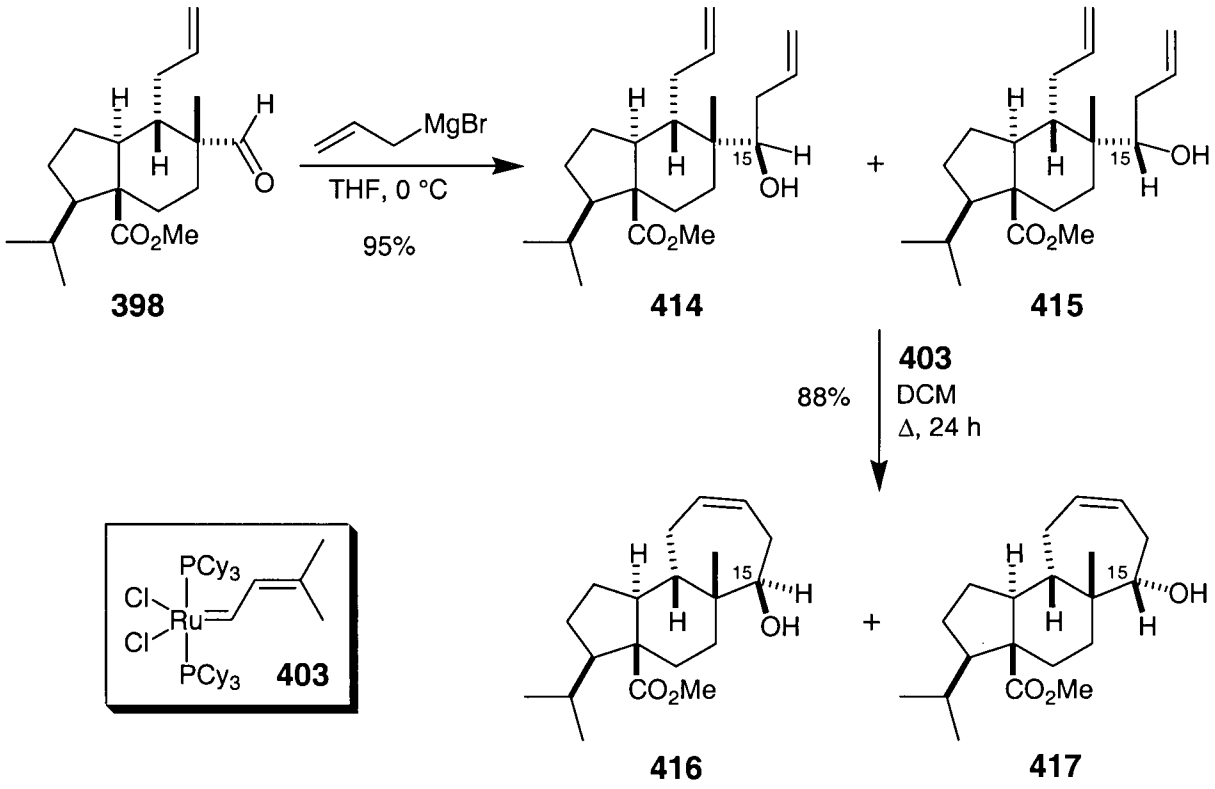
Note that when catalyst **403** is used, the catalytic species after the first cycle is compound **404**. Therefore it was expected that the reaction mechanism depicted in **Scheme 3.97** would operate during the planned ring-closing metathesis.



Scheme 3.97: Major catalytic pathway for the ring-closing metathesis of diene 405 using catalyst 404[178]

The minor catalytic pathway is very similar to that depicted in **Scheme 3.97**. It differs in that all the ligands in the catalyst (**404**) remain bound to the metal center throughout the catalytic cycle.

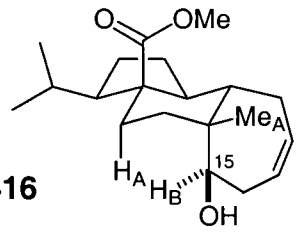
Treatment of aldehyde **398** with allyl magnesium bromide provided a nearly 1:1 mixture of homoallylic alcohols epimeric at C-15 (mulinane numbering, **414** and **415**, **Scheme 3.98**). Although these alcohols could be separated on TLC, they were carried on to the next step as a mixture. Thus, subjection of alcohols **414** and **415** to ring-closing metathesis reaction conditions provided a mixture of tricyclic alcohols **416** and **417**.



Scheme 3.98: Preparation of tricyclic alcohols 416 and 417 from aldehyde 398

Alcohols **416** and **417** were easily separated by flash column chromatography on silica gel. The ^{1}H NMR spectrum of alcohol **416** exhibited a two proton multiplet at δ = 5.62-5.76 which accounted for the alkenyl protons. The carbinol proton was observed as a one-proton broad doublet at δ = 3.84-3.92 (J = 11.4 Hz). The ^{13}C NMR displayed two alkenyl carbon resonances at δ = 127.7 and δ = 131.2. A J-mod ^{13}C NMR experiment demonstrated the presence of six methylene groups and a total of eleven methyl and methine groups. The relative configuration of the carbon chirality center at C-15 (mulinane numbering) was determined to be as shown based on an NOE difference experiment (see **Figure 3.34**).

The ^{1}H NMR spectrum of alcohol **417** displayed two one-proton resonances at δ = 5.63-5.71 and δ = 5.82-5.91 which were attributed to the alkenyl protons. The carbinol proton resonated at δ = 3.46-3.53 (dd; J = 7.0, 7.0 Hz). The ^{13}C NMR spectrum contained two alkenyl carbon resonances at δ = 127.7 and δ = 132.7. A *J*-mod ^{13}C NMR experiment demonstrated the presence of six methylene groups and a total of eleven methyl and methine groups. The relative configuration of the carbon chirality center at C-15 (mulinane numbering) was assigned to be as shown based on an NOE difference experiment (see **Figure 3.34**).



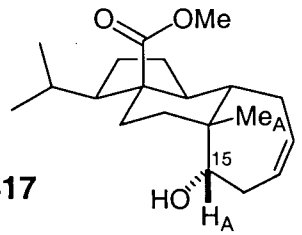
416

H_A: δ = 1.00-1.10
(ddd, J = 14.6, 14.6, 3.7 Hz)

H_B: δ = 3.84-3.92
(br. d, J = 11.4 Hz)

Me_A: δ = 0.98 (s)

irradiation of H_B enhances H_A,
does not enhance Me_A



417

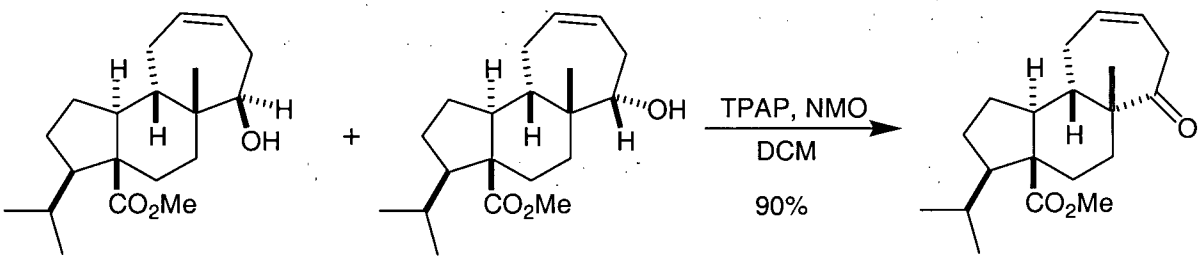
H_A: δ = 3.46-3.53
(dd J = 7.0, 7.0 Hz)

Me_A: δ = 0.90 (s)

irradiation of H_A enhances Me_A

Figure 3.34: Selected NOE difference data for alcohols 416 and 417

Tricyclic alcohols **416** and **417** converged to enone **402** upon oxidation using Ley's method (see **Scheme 3.99**). Due to a fortuitous dispersion of signals, the ^{1}H NMR spectrum of enone **402** could be fully assigned. The alkenyl protons gave rise to two one-proton multiplets at δ = 5.67-5.76 and δ = 5.79-5.88. The C-11 methylene protons were observed as a one-proton multiplet at δ = 3.67-3.74 and a one-proton doublet of doublets at δ = 2.62-2.71 (J = 12.7, 8.7 Hz). The ^{13}C NMR spectrum of contained two alkenyl carbon resonances at δ = 123.8 and δ = 131.4. The ketone carbonyl carbon resonated at δ = 208.4. A J-mod ^{13}C NMR experiment verified the presence of six methylene groups and a total of ten methyl and methine groups.



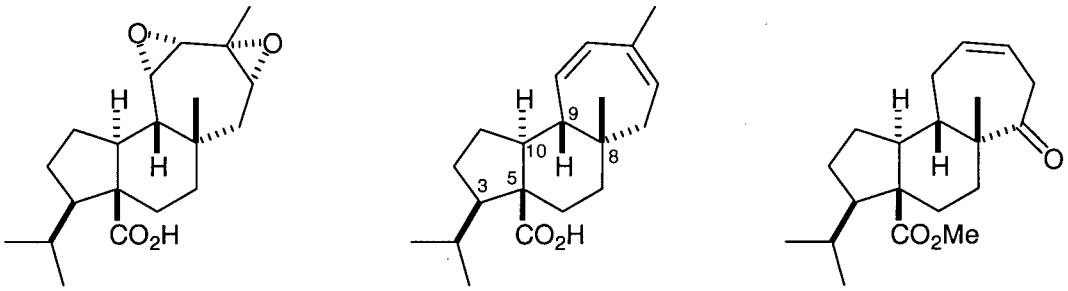
416 **417** **402**

Scheme 3.99: Preparation of β,γ unsaturated ketone 402

At this point, due to time constraints and in consideration of the expected difficulties in accessing the mulinane family of diterpenoids from compound **402**, the proposed synthesis of (±)-isomulinic acid was abandoned.

3.5 Summary

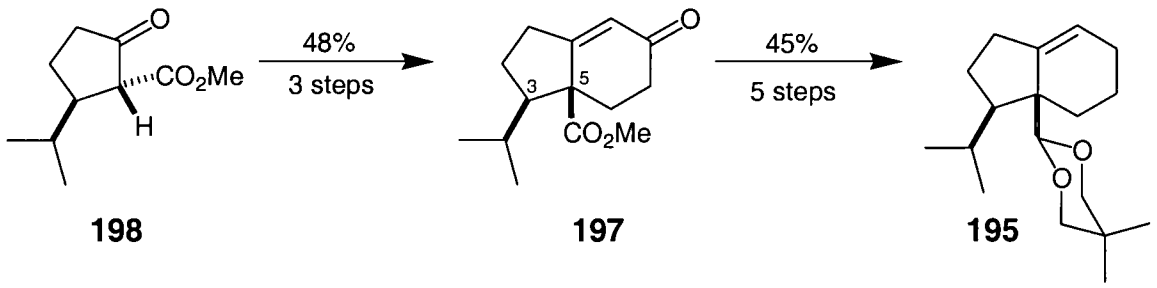
The total synthesis of isomulinic acid (**39**, **Figure 3.35**) was attempted in racemic form. The natural product mulin-11,13-dien-20-oic acid (**157**) was identified as a key intermediate *en route* to isomulinic acid. Four distinct synthetic approaches were explored but none provided access to the mulinane carbocyclic framework. Each approach provided insights which influenced the design of the next. The final synthetic approach allowed access to tricyclic enone **402** in a total of 23 linear steps from a known compound. Note that tricycle **402** possesses all the carbon chirality centers present in mulin-11,13-dien-20-oic acid (**157**) with the correct relative configuration.



39 **157** **402**

Figure 3.35: Structures of isomulinic acid (39), mulin-11,13-dien-20-oic acid (157) and tricyclic enone 402

The first synthetic plan incorporated the seven-membered ring annulation method developed in this laboratory as a key step.[34] The known keto ester **198**[114] was prepared in three steps from commercially available materials (**Scheme 3.100**). Bicyclic enone **197** was constructed from keto ester **198** in three steps and served as a platform for all four synthetic approaches. Note that the carbon chirality centers at C-3 and C-5 of enone **197** possess the correct relative configuration. Alkene **195** was prepared from enone **197** in five steps using standard methods.

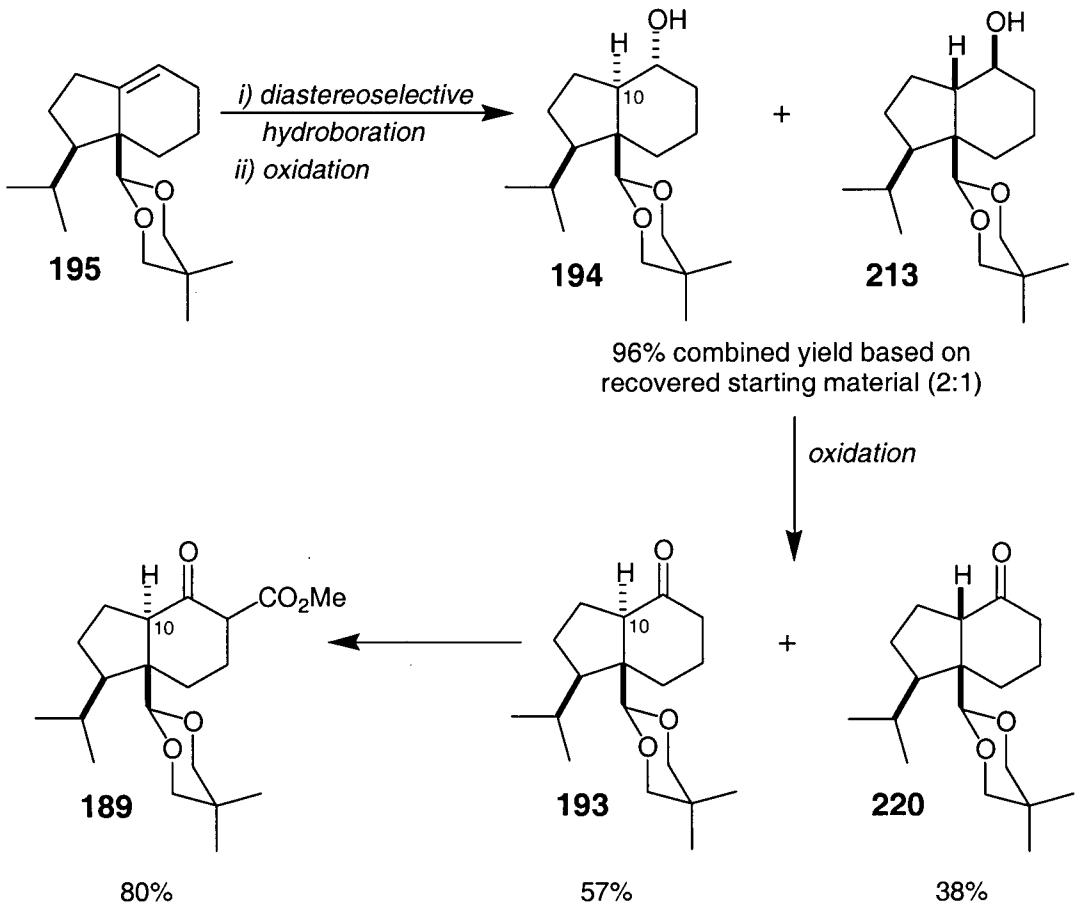


198 197 195

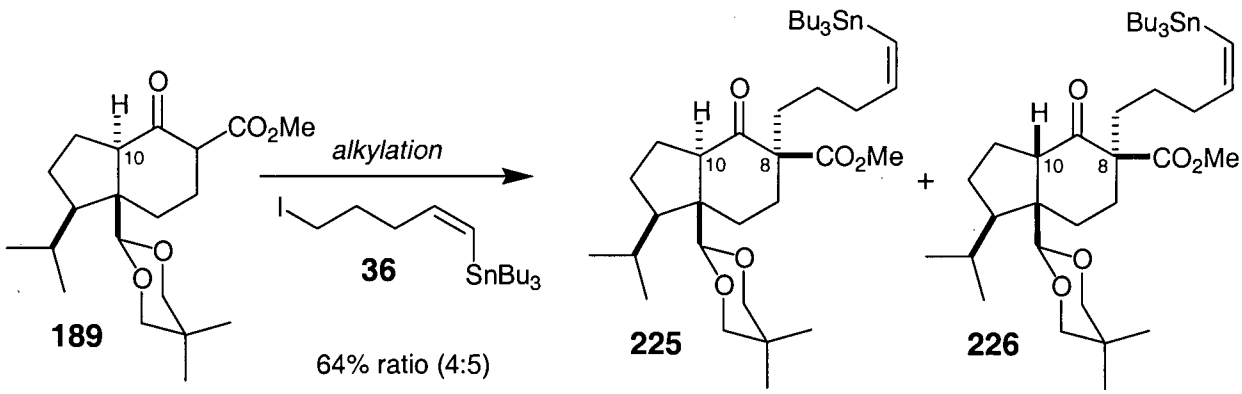
Scheme 3.100: Preparation of alkene 195

A diastereoselective hydroboration reaction of alkene **195** was used to establish the carbon chirality center at C-10 of alcohol **194** (**Scheme 3.101**). Unfortunately, the diastereoselectivity of this reaction was poor. Furthermore, alcohols **194** and **213** proved difficult to separate and were, therefore, oxidized to the corresponding ketones (**193** and **220**) as a mixture. Note that the carbon chirality center at C-10 of ketone **193** is configurationally stable under the oxidation conditions. Ketones **193** and **220** were easily separated and ketone **193** was elaborated to keto ester **189**.

It could be shown that the alkylation of keto ester **189** proceeds with a high degree of diastereoselectivity to establish the carbon chirality center at C-8 (**Scheme 3.102**). Unfortunately, the alkylation of keto ester **189** with the bifunctional reagent *cis*-5-iodo-1-tri-*n*-butylstannylpent-1-ene (**36**) provided a mixture of keto esters **225** and **226**, which are epimeric at C-10. Evidently the desired product is configurationally unstable under the alkylation conditions. The failure to prepare alcohol **194** in high yield from alkene **195**, and the configurational instability of keto ester **225** caused us to abort this synthetic plan.

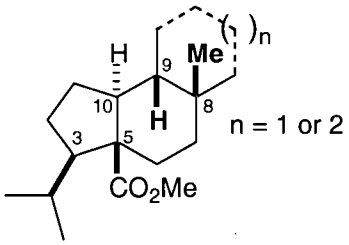


Scheme 3.101: Preparation of keto ester 189

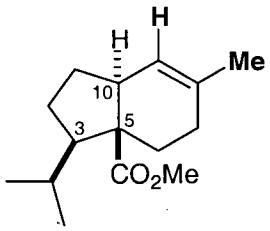


Scheme 3.102: Alkylation of keto ester 189 with bifunctional reagent 36

The second synthetic approach focused on trying to gain expedient access to a tricyclic substance, exemplified by the general structure **229**, which possesses the requisite carbon chirality centers with the correct relative configuration (**Figure 3.36**). It was envisioned that the carbon chirality centers at C-8 and C-9 of tricycle **229** would be established through a highly diastereo- and regioselective [2+2]-photocycloaddtion reaction between alkene **228** and a suitable partner. Thus, the synthetic plan focused on gaining access to bicycle **228**, which possesses the correct relative configuration at C-10.



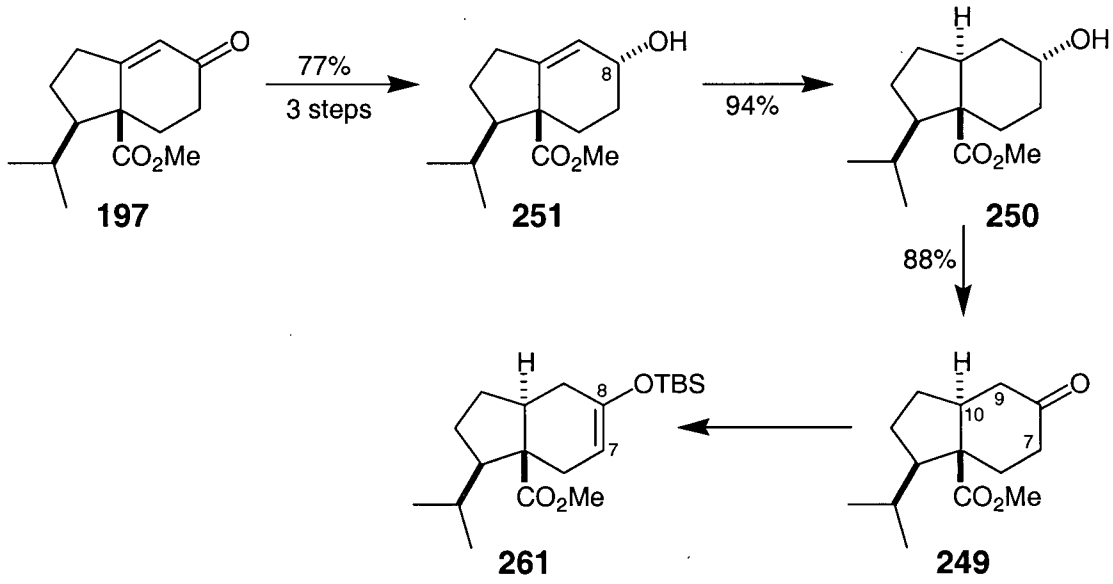
229



228

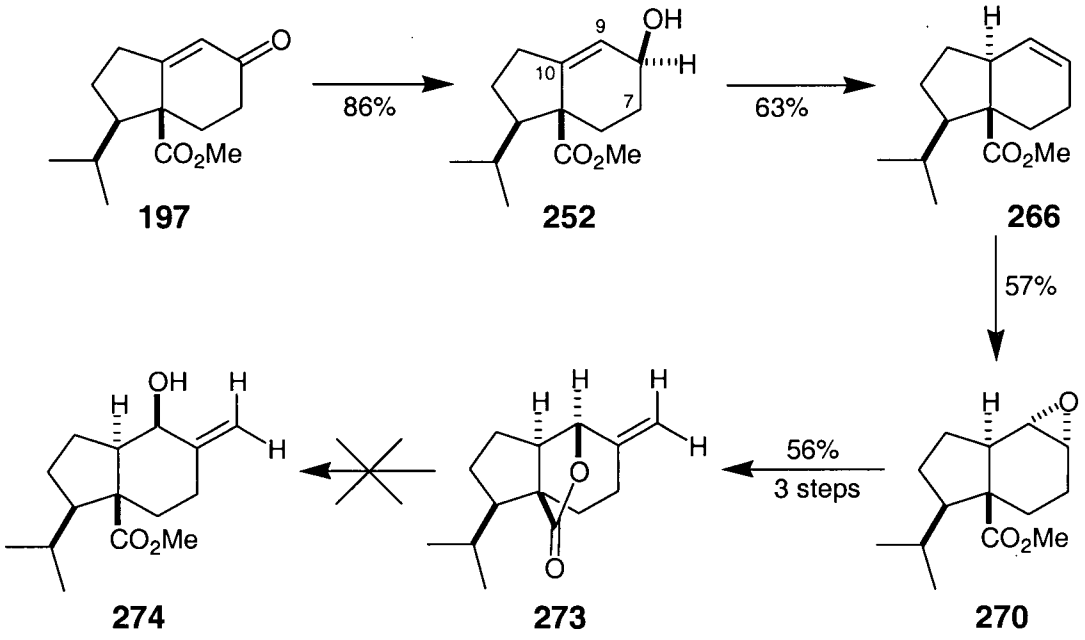
Figure 3.36: Structures of tricycle 229 and alkene 228

Bicyclic enone **197** was efficiently converted to allylic alcohol **251** using standard methods (**Scheme 3.103**). The hydroxyl group at C-8 of alcohol **251** was utilized to direct the hydrogenation of the double bond and thus provide access to alcohol **250**. This material was oxidized to ketone **249**. The formation of the thermodynamic enolate of ketone **249**, followed by treatment with a sililating agent, provided silyl enol ether **261**, in which the carbon-carbon double bond resides between C-7 and C-8, as the major product. This indicated that it would be difficult to establish the desired double bond between C-8 and C-9 of alkene **228**.



Scheme 3.103: Preparation of silyl enol ether 258

An alternate route to alkene **228** was devised. This strategy allowed for the selective activation of C-9 versus C-7. Thus, enone **197** was reduced to alcohol **252** (**Scheme 3.104**). This material was transformed to alkene **266** using the method developed by Myers and Zheng.[133] The diasteroselective epoxidation of alkene **266** provided oxirane **270**. A three step sequence inspired by the work of Barrero[138] provided access to bridged lactone **273**. It was hoped that methanolysis of lactone **273** would provide access to allylic alcohol **274** which could, in principle, yield alkene **228** through the use of Myers' method.[133] Unfortunately, compound **273** proved unreactive under methanolysis conditions. The stability of lactone **273** coupled with an interest in exploring a more expedient route to the mulinane natural products led us to abandon this synthetic approach.

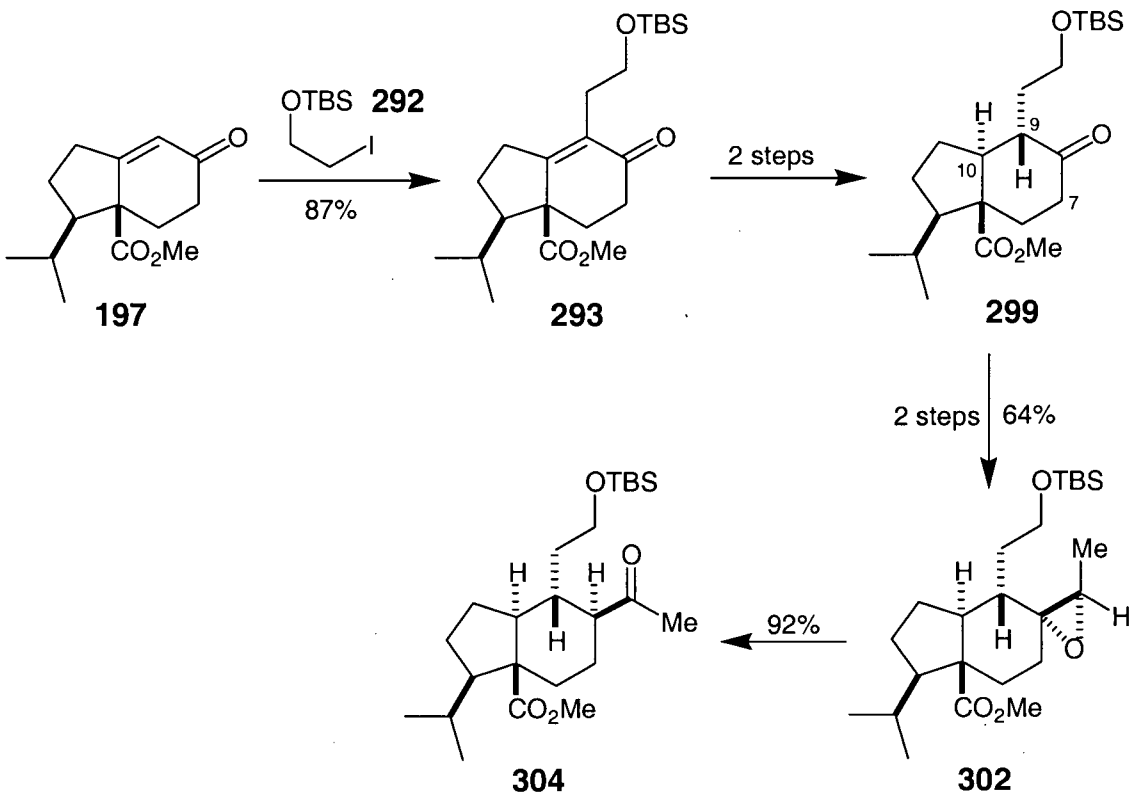


Scheme 3.104: Preparation of lactone 273

The results obtained from the second synthetic approach demonstrated that it was necessary to differentiate between C-7 and C-9 prior to establishing the carbon chirality center at C-10. A report by McKenzie[139] indicated that *trans*-fused hydrindane systems bearing an alkyl substituent at C-9 could be obtained through the heterogeneous hydrogenation of the corresponding enones. It was realized that if Mackenzie's mechanistic rationale held true when applied to an enone such as **293** (see **Scheme 3.105**), it would provide expedient access to a hydrindane system which possessed four of the five requisite carbon chirality centers with the correct relative configuration (**299**). The fifth carbon chirality center was expected to be installed using Yamamoto's procedure for the rearrangement of trisubstituted oxiranes to tertiary aldehydes.[140]

The thermodynamic enolate of ketone **197** was alkylated with iodide **292** to provide enone **293** (**Scheme 3.105**). The hydrogenation of **293** under heterogeneous conditions led to undesired sideproducts when carried out in large scale. However, small scale reactions provided sufficient material to further explore the synthetic plan. Subjection of the material acquired from the hydrogenation reaction to equilibrating conditions furnished ketone **299**. Note that this compound possesses four of the

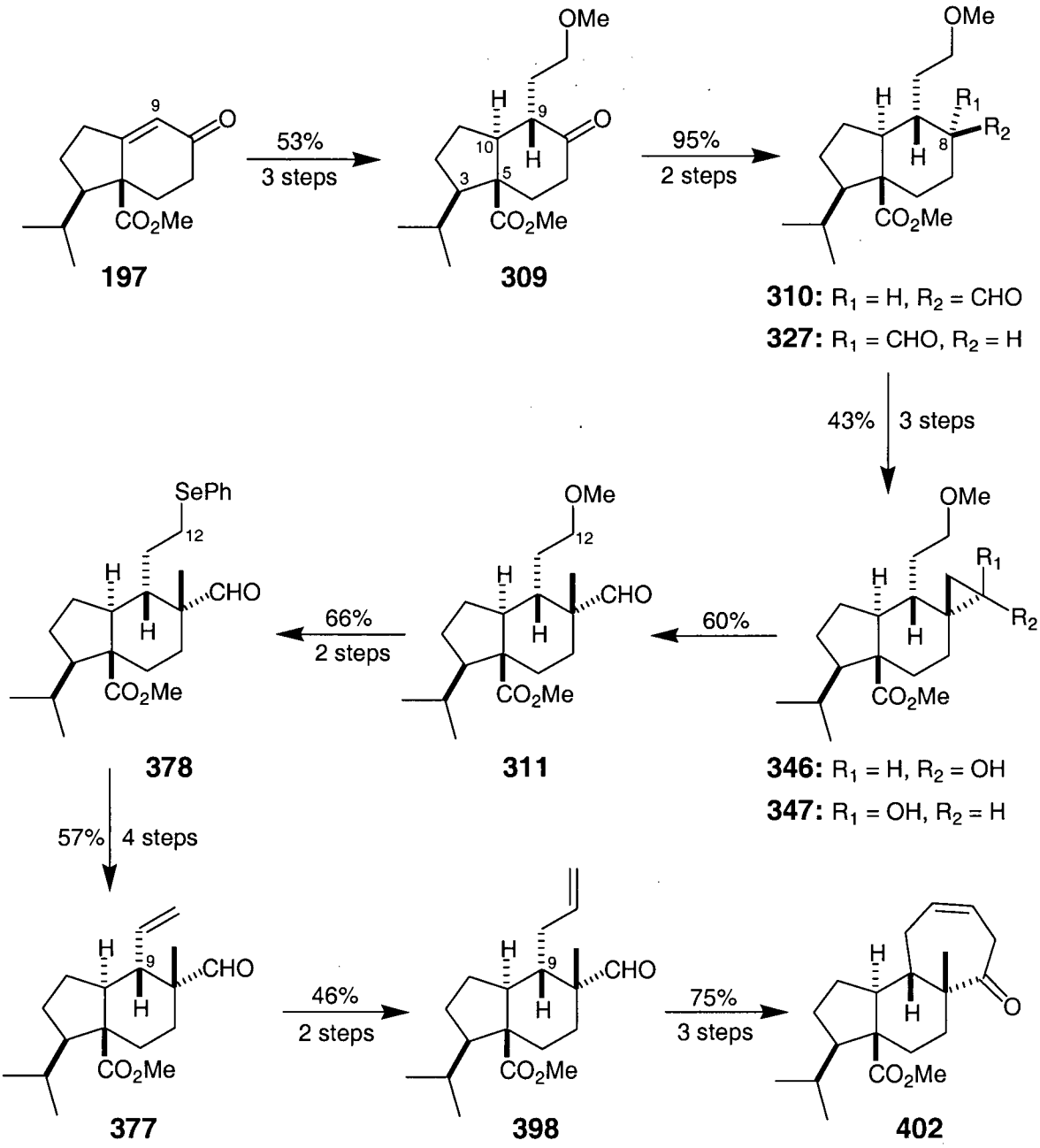
requisite carbon chirality centers with the correct relative configuration. Wittig olefination of ketone **299**, followed by epoxidation of the acquired alkene furnished oxirane **302**. Unfortunately, treatment of this epoxide with Yamamoto's Lewis acid provided ketone **304** as the major product.



Scheme 3.105: Preparation of ketone 304

The exploration of this synthetic approach demonstrated that a *trans*-fused hydrindanone with four of the requisite carbon chirality centers, such as **299**, could be prepared in an expedient fashion. Clearly, the hydrogenation process required some modifications. It was evident that the *tert*-butyldimethyl silyl protecting group was too labile under the hydrogenation conditions. Therefore, it was decided to replace it with a methyl group in the fourth and final approach explored.

As expected, the alkylation of enone **197** with 2-bromoethyl methyl ether provided the required C-9 alkylated enone (not shown). Hydrogenation of this enone, followed by equilibration of the acquired material, provided ketone **309** (**Scheme 3.106**). Note that bicycle **309** possesses the correct relative configuration at C-3, C-5, C-9 and C-10. Ketone **309** was converted to a mixture of spiroepoxides (not shown) using the Corey-Chaykovsky protocol.[154,155] Treatment of this mixture of epoxides with Yamamoto's Lewis acid[140] provided an inseparable mixture of aldehydes **310** and **327**, which are epimeric at C-8. The direct alkylation of aldehydes **310** and **327** to establish the carbon chirality center at C-8 failed under a variety of conditions. Therefore a reaction sequence which relied on the known rearrangement of cyclopropanols to α-methyl aldehydes[160-165] was used to establish the C-8 quaternary center. Thus, aldehydes **310** and **327** were converted to a mixture of spirocyclopropanols **346** and **347** in three steps. Alcohols **346** and **347** converged to aldehyde **311** upon treatment with a Brønsted acid in hot THF. Note that aldehyde **311** possesses all five carbon chirality centers present in all the members of the mulinane family of diterpenoids, with the correct relative configuration.



Scheme 3.106: Final synthetic approach to the (±)-isomulinic acid

Having obtained access to aldehyde **311**, all efforts were focused on establishing the third ring of the mulinane carbocyclic skeleton. Treatment of aldehyde **311** with TMSI[150] provided the corresponding C-12 iodide (not shown). This material was converted to phenylselenide **378** using Sharpless' protocol. The preparation of alkene **377** from phenylselenide **378** required a four-step sequence. An unexpected rearrangement occurred when the homologation of aldehyde **377** was attempted.

Conversion of aldehyde **377** to a mixture of spiroepoxides, followed by treatment of this mixture with a Lewis acid resulted in the conversion of the C-9 vinyl group to an allyl group. Finally, it could be shown that the seven-membered ring could be constructed using a sequence of reactions which included a ring-closing diene metathesis as a key step.

Unfortunately, due primarily to time constraints, the total synthesis of (±)-isomulinic acid (**39**) or any other member of the mulinane family of diterpenoids was not achieved. However, it could be shown that the hydrindane system embedded in the mulinane carbocyclic skeleton, with the correct relative configuration at all five carbon chirality centers, could be accessed in an efficient and expedient manner (see **311**, **Scheme 3.106**). Furthermore, the seven-membered ring could be constructed using a strategy which included a ring-closing diene metathesis as a key step. Unfortunately, due to an unexpected rearrangement reaction that occurred during the attempted homologation of aldehyde **377**, the position of the functional groups on the seven-membered ring of tricyclic enone **402** was not conducive to an expedient construction of (±)-isomulinic acid (**39**).

4. Experimental

4.1 General

4.1.1 Data acquisition, presentation and experimental techniques

All reported compounds have been given systematic names according to the IUPAC protocol for bridged carbocycles.[90,91]

Melting points were recorded on a Fischer-Johns melting point apparatus.

Infrared (IR) spectra were recorded as thin films between sodium chloride plates employing a Perkin-Elmer 1710 FT-IR spectrophotometer with internal calibration.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker spectrometer models AMX-500 (500 MHz), WH-400 (400 MHz), AV-400 (400 MHz) or AV 300 (300 MHz) using deuteriochloroform ($CDCl_3$) as the solvent.[179,180] Signal positions (δ values) are reported in parts per million (ppm) from tetramethylsilane ($\delta = 0$) and were measured relative to the signal for chloroform ($\delta = 7.24$). Whenever possible, the ^{1}H coupling constants (*J* values) were determined using the guidelines to first-order multiplet analysis reported by Hoye *et al.*[181,182] Coupling constants are reported in Hertz (Hz). The tin-proton coupling constants ($J_{Sn\text{-}H}$) are reported as an average of the ^{117}Sn and the ^{119}Sn values. The spectral data are reported in the following format: chemical shift (ppm), multiplicity, number of protons, coupling constants(s), and assignments (when known). The abbreviations used for multiplicities are: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). In some cases, the proton assignments were supported by COSY (^{1}H-^{1}H homonuclear correlation spectroscopy) and/or 1D-NOED (one dimensional nuclear Overhauser enhancement difference) experiments.

Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker spectrometer models AMX-500 (125.8 MHz), AV-400 (100.4 MHz) or AV 300 (75.5 MHz) using deuteriochloroform as the solvent. Signal positions (δ values) are

reported in parts per million (ppm) from tetramethylsilane (δ = 0) and were measured relative to the signal for chloroform (δ = 77.0). In some cases, *J*-modulated spin-echo experiments (also called attached proton test (APT) experiments) were used to differentiate the signals due to methyl and methine groups from the signals due to methylene groups and quaternary carbons. The ATP spectra were phased such that the signals due to methyl and methine groups are negative (−ve) and the signals due to methylene groups and quaternary carbons are positive (+ve). In some cases, the proton and carbon assignments were supported by (^{1}H, ^{13}C) heteronuclear multiple quantum coherence (HMQC) experiments and heteronuclear multiple bond correlation (HMBC) experiments, which were carried out on a Bruker AMX-500 spectrometer or a Bruker AV-400 spectrometer.

Coupled gas chromatography-low resolution mass spectrometry analyses (GC-MS) were carried out on an Agilent 6890 series gas chromatograph equipped with an HP-5 column (cross-linked 5% diphenyl, 95% dimethylpolysiloxane, length: 30 m, internal diameter: 0.25 mm, film thickness: 0.25 µm) and coupled to an Agilent 5973*Network* mass selective detector.

High resolution electron impact mass spectra (HREIMS) were recorded on a Kratos MS80 or on a Kratos Concept II HQ mass spectrometer. The molecular ion [M^{+}] masses are reported unless otherwise noted. All compounds subjected to high resolution mass measurements were homogeneous by TLC and/or GC-MS analysis.

Thin layer chromatography (TLC) analyses were carried out on commercially available aluminium-backed silica gel 60 F_{254} plates (E. Merck or Macherey-Nagel brand, thickness: 0.2 mm). Visualization was accomplished by using uv light (254 nm) and/or staining the plates with one of the following reagents: a) phosphomolybdic acid (PMA) in EtOH (20% w/v, Aldrich Chemical Co.), b) ammonium molybdate (5% w/v) and cerium(IV) sulfate (0.1% w/v) in 10% aqueous sulfuric acid, c) vanillin (6% w/v) in sulfuric acid (4% v/v)-EtOH (10% water v/v in EtOH).

Purifications by flash column chromatography were performed using 230-400 mesh silica gel (SiliCycle) following the technique described by Still.[183]

All reactions which are sensitive to moisture were carried out using flame- or oven-dried glassware under an atmosphere of dry argon. Glass syringes, Teflon® cannulae and stainless steel needles used to handle dry solvents and reagents were oven dried, cooled in a dessicator, and flushed with argon prior to use. Sub-milliliter volumes of reagents were measured using gas-tight™ microliter syringes which had been dried under reduced pressure (vacuum pump) and stored in a dessicator prior to use.

Concentration, evaporation, or removal of solvent under reduced pressure (water aspirator) refers to solvent removal using a Büchi rotary evaporator at 20-25 Torr. Removal of solvents using fractional distillation at atmospheric pressure was carried out using a Vigreux column (length: 100 mm, internal diameter: 10 mm).

Cold temperatures were maintained using one of the following: 10 °C; Julabo cryobath (model FP80), 0 °C, ice-water bath or Julabo cryobath (model FP80); –30 °C, aqueous $CaCl_2$-dry ice (35 g $CaCl_2$/100 mL H_2O);[184] –78 °C, acetone-dry ice or Julabo cryobath (model FP80).

4.1.2 Solvents and reagents

All solvents and reagents were purified using established procedures.[185] Benzene, DCM, pentane, and DME were distilled from calcium hydride. Et_2O and THF were distilled from sodium benzophenone ketyl. All of these solvents were distilled under an atmosphere of dry argon and used immediately. Methanol was distilled from Mg with a catalytic amount of I_2 under an atmosphere of nitrogen.

Methyl vinyl ketone was distilled prior to use. Iodomethane and diiodomethane were passed through a short column of oven dried basic alumina prior to use. Diisopropylamine and BF_3•Et_2O were distilled from calcium hydride under an atmosphere of argon.

MABR was prepared using the procedure developed by Yamamoto and coworkers.[140] NBSH was prepared using the method of Myers.[136] DMDO was prepared using the protocol outlined by Adam *et al.*[186]

Solutions of LDA were prepared by adding a solution of butyllithium (1.0 equiv.) in hexanes to a solution of freshly distilled diisopropylamine in THF at –78 °C, followed by warming to 0 °C for 20 min prior to use.

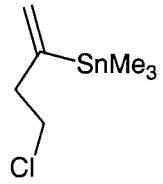
Petroleum ether refers to a hydrocarbon mixture with a boiling point range of 30-60 °C

Argon and nitrogen were dried by bubbling the gas through concentrated sulfuric acid and then passing it through a column of Drierite® and potassium hydroxide.

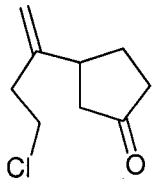
All other solvents and reagents were commercially available and were used without further purification.

4.2 Experimental – Total Synthesis of (±)-Kelsoene

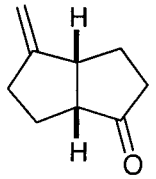
3-(4-Chlorobut-1-en-2-yl)cyclopentanone (118) and (1*R**, 5*S**)-6-methylidenebicyclo[3.3.0]octan-2-one (*rac*-34).



32



118

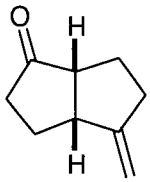


***rac*-34**

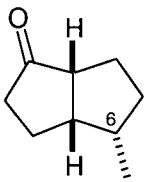
To a cold (−78 °C) stirred solution of 4-chloro-2-trimethylstannylbut-1-ene (**32**) (7.08 g, 27.9 mmol) in dry THF was added MeLi (1.6 M solution in Et_2O, 19 mL, 30.5 mmol) and the mixture was stirred at −78 °C for 5 min. A solution of CuCN (2.71 g, 30.3 mmol) and LiCl (1.29 g, 30.3 mmol) in dry THF (35 mL) was added and the solution was stirred at −78 °C for 5 min. BF_3•Et_2O (3.79 mL, 29.9 mmol) was added dropwise over 10 min and the solution was stirred at −78 °C for 15 min. Freshly distilled cyclopent-2-en-1-one (2.79 mL, 33.4 mmol) was added and the mixture was stirred at −78 °C for 1 h. Sat. aq NH_4Cl (30 mL) was added and the stirred mixture was allowed to warm to r.t. The phases were separated and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed (brine, 30 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (400 g of silica gel, 5:1 petroleum ether−Et_2O) of the crude oil afforded compound **118** as a colourless oil that displayed ^1H NMR spectral data in accordance with that previously reported in the literature; [32] yield: 3.84 g (79%).

Conversion of the chloroketone **118** into the bicyclic ketone ***rac*-34** was accomplished by treatment of the former substance with KH in THF as previously described.[32]

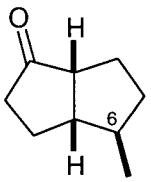
(1*R,5*S**,6*S**)-6-Methylbicyclo[3.3.0]octan-2-one (*rac*-59) and (1*R**,5*S**,6*R**)-6-methylbicyclo[3.3.0]octan-2-one (119)**



***rac*-34**



***rac*-59**



119

To a solution of ketone ***rac*-34** (2.235 g, 16.4 mmol) in DCM (120 mL) was added chlorotris(triphenylphosphine)rhodium(I) (Wilkinson's catalyst, 106 mg, 0.11 mmol). The solution was stirred at r.t. under an atmosphere of hydrogen (~760 torr) for 48 h. The solution was filtered through a pad of silica gel (25 g, elution with DCM) and the filtrate was concentrated via fractional distillation. Flash chromatography (200 g of silica gel, 7:1 pentane–Et_2O) of the remaining material provided a colourless oil that consisted of a mixture of ketones ***rac*-59** and its C-6 epimer **119** (ratio = 95:5 by ^1H NMR spectroscopy); yield: 2.15 g (95%).

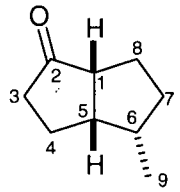
IR (film): ν = 2953, 2874, 1736, 1459, 1161, 1107 cm^{-1}.

^1H NMR (500 MHz): δ = 0.97 (d, 3 H, J = 6.9 Hz), 1.12 (m, 1 H), 1.48 (dddd, 1 H, J = 13.0, 11.4, 9, 8.3 Hz), 1.62 (dddd, 1 H, J = 12.7, 6, 6, 3 Hz), 1.77-1.83 (m, 2 H), 1.84 (dddd, 1 H, J = 13.0, 9.4, 3.4,1.0 Hz), 2.03-2.13 (m, 1 H), 2.17 (ddd, 1 H, J = 17.6, 8.3, 3.4 Hz), 2.25 (dddd, 1 H, J = 17.6, 11.4, 9.4, 1.4 Hz), 2.58 (ddd, 1 H, J = 9, 9, 5.0 Hz), 2.66 (m, 1 H).

^{13}C NMR (125 MHz): δ = 14.2, 21.4, 28.8, 32.3, 38.3, 39.6, 45.0, 51.7, 223.1.

Exact mass calculated for $C_9H_{14}O$: 138.1045; found 138.1044.

Table 4.1. NMR data for (1*R**,5*S**,6*S**)-6-methylbicyclo[3.3.0]octan-2-one (***rac*-59**)



Carbon No.	^{13}C δ (ppm)[a]	1H δ (ppm)(mult; *J* (Hz))[b,c,d]	HMBC Correlations[b,e]
1	51.7	H-1: 2.58 (ddd; 9,9,5.0)	H-5, H-8a, H-8b
2	223.1		H-1, H-3a, H-3b, H-4b
3	39.6	H-3a: 2.17 (ddd; 17.6, 8.3, 3.4)	
		H-3b: 2.25 (dddd; 17.6, 11.4, 9.4, 1.4)	
4	21.4	H-4a: 1.48 (dddd; 13.0, 11.4, 9, 8.3)	H-1, H-3a, H-3b, H-5, H-6
		H-4b: 1.84 (dddd; 13.0, 9.4, 3.4, 1.0)	
5	45.0	H-5: 2.66 (m)	H-3a, H-3b, H-4a, H-4b, H-6, H-7, H-9
6	38.3	H-6: 2.03-2.13 (m)	H-4a, H-7b, H-8a, H-8b, H-9
7	32.3	H-7a: 1.12 (m)	H-5, H-6, H-8a, H-8b, H-9
		H-7b: 1.62 (dddd; 12.7, 6, 6, 3)	
8	28.8	H-8a: part of the m at 1.77-1.83 (m)	H-1, H-5, H-6, H-7b
		H-8b: part of the m at 1.77-1.83 (m)	
9	14.2	0.97 (d; 6.9)	H-6, H-7a

[a] Recorded at 125 MHz.

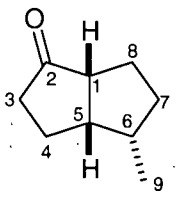
[b] Recorded at 500 MHz.

[c] Assignments based on HMQC data recorded at 500 MHz.

[d] Methylene protons are designated H-Xa and H-Xb arbitrarily.

[e] Only those correlations which could be unambiguously assigned are recorded.

Table 4.2. NMR data for (1*R**,5*S**,6*S**)-6-methylbicyclo[3.3.0]octan-2-one (***rac*-59**)



Proton No.	1H δ (ppm)(mult; *J* (Hz))[a,b,c]	COSY Correlations[a,d]
H-1	2.58 (ddd; 9,9,5.0)	H-8a, H-8b
H-3a	2.17 (ddd; 17.6, 8.3, 3.4)	H-3b, H-4a, H-4b
H-3b	2.25 (dddd; 17.6, 11.4, 9.4, 1.4)	H-3a, H-4a, H-4b
H-4a	1.48 (dddd; 13.0, 11.4, 9 ,8.3)	H-3a, H-3b, H-4b, H-5
H-4b	1.84 (dddd; 13.0, 9.4, 3.4, 1.0)	H-3a, H-3b, H-4a, H-5
5	2.66 (m)	H-4a, H-4b, H-6
6	2.03-2.13 (m)	H-5, H-9
H-7a	1.12 (m)	H-7b, H-8a, H-8b
H-7b	1.62 (dddd; 12.7, 6, 6, 3)	H-7a, H-8a, H-8b
H-8a	part of the m at 1.77-1.83 (m)	H-1, H-7a, H-7b
H-8b	part of the m at1.77-1.83 (m)	H-1, H-7a, H-7b
9	0.97 (d; 6.9)	H-6

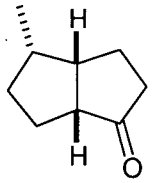
[a] Recorded at 500 MHz.

[b] Assignments are based on HMQC data recorded at 500 MHz.

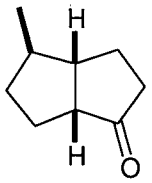
[c] Methylene protons are designated H-Xa and H-Xb arbitrarily.

[d] Only those correlations which could be unambiguously assigned are recorded.

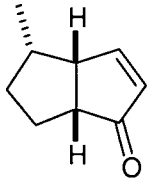
(1*R,5*R**,6*S**)-6-Methylbicyclo[3.3.0]oct-3-en-2-one (*rac*-60)**



***rac*-59**



119



***rac*-60**

To a cold (−78 °C) solution of LDA (0.321 M in THF, 25 mL, 8.03 mmol) was added a cold (−78 °C) solution of ketones ***rac*-59** and **119** (0.923 g, 6.69 mmol) in THF (20 mL). The solution was warmed to 0 °C for 30 min and then was cooled to −78 °C. A cold (−78 °C) solution of phenylselenenyl chloride (1.60 g, 8.35 mmol) in THF (10 mL) was added, the mixture was stirred at −78 °C for 1 h, and then was treated with 10% aq HCl (10 mL). The phases were separated and the organic phase was washed (brine, 10 mL), dried ($MgSO_4$) and concentrated. The crude product was dissolved in DCM (20 mL) and the solution was cooled to 0 °C. Aq H_2O_2 (8.8 M, 1.5 mL, 13 mmol) was added, the mixture was stirred for 1 h, and then was treated with 10% aq HCl (10 mL). The phases were separated and the organic phase was washed (sat. aq $NaHCO_3$, 10 mL), dried ($MgSO_4$) and concentrated by fractional distillation. Flash chromatography (80 g of silica gel, 5:1 pentane−Et_2O) of the crude oil provided enone ***rac*-60** as a colourless oil; yield: 0.755 g (83%). No attempt to identify or isolate the product derived from ketone **119** was made.

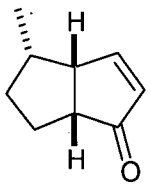
IR (film): ν = 2954, 2873, 1707, 1585, 1459, 1353, 1187, 732 cm^{-1}.

^1H NMR (400 MHz): δ = 0.83-0.91 (m, 1 H), 1.01 (d, 3 H, J = 7.0 Hz), 1.49-1.57 (m, 1 H), 1.63-1.75 (m, 1 H), 1.84 (dd, 1 H, J = 12.6, 6.4 Hz), 1.97-2.01 (m, 1 H), 2.63 (dd, 1 H, J = 10.4, 5.5 Hz), 3.23 (dddd, 1 H, J = 8.5, 5.5, 2.7, 2.7 Hz), 6.17 (dd, 1 H, J = 5.8, 2.7 Hz), 7.57 (dd, 1 H, J = 5.8, 2.7 Hz).

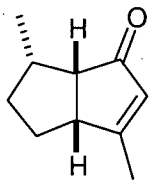
^{13}C NMR (100 MHz): δ = 15.7, 28.9, 31.3, 36.8, 49.9, 50.2, 135.8, 165.3, 213.7.

Exact mass calculated for $C_9H_{12}O$: 136.0888; found 136.0893.

(1*S,5*R**,8*S**)-4,8-Dimethylbicyclo[3.3.0]oct-3-en-2-one (*rac*-61)**



***rac*-60**



***rac*-61**

To a cold (−78 °C) solution of enone ***rac*-60** (0.872 g, 6.41 mmol) in Et_2O (30 mL) was added MeLi (1.6 M solution in Et_2O, 4.5 mL, 7.2 mmol) and the mixture was allowed to warm to r.t. over a period of 1 h. The solution was treated with tris(hydroxymethyl)aminomethane buffer (pH = 8, 0.5 M, 20 mL) and the phases were separated. The organic phase was washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The remaining crude oil was dissolved in DCM (40 mL) and the solution was cooled to 0 °C. Pyridinium chlorochromate adsorbed on basic alumina (0.79 mmol/g, 12 g, 9.5 mmol) was added to the solution in one portion and the resulting slurry was stirred for 4 h. The mixture was filtered through a pad of Florisil® (60 g, elution with 100 mL of Et_2O). The filtrate was concentrated by fractional distillation and the residual oil was purified by flash chromatography (50 g of silica gel, 3:1 pentane–Et_2O) to provide enone ***rac*-61** as a colourless oil; yield: 0.557 g (60 %).

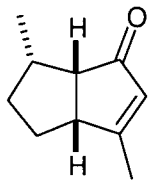
IR (film): ν = 2953, 1699, 1622, 1439, 1379, 1273, 1190, 882 cm^{-1}.

^1H NMR (400 MHz): δ = 0.95-1.01 (m, 1 H), 1.03 (d, 3 H, J = 7.0 Hz), 1.57-1.72 (m, 3 H), 2.01-2.10 (m, 1 H), 2.02 (s, 3 H), 2.60 (dd, 1 H, J = 9.9, 5.6 Hz), 3.08-3.15 (m, 1 H), 5.82-5.84 (m, 1 H).

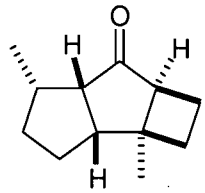
^{13}C NMR (100 MHz): δ = 15.6, 17.5, 27.7, 32.3, 37.0, 50.9, 53.7, 132.4, 179.6, 210.2.

Exact mass calculated for $C_{10}H_{14}O$: 150.1045; found 150.1048.

(1*R,2*S**,5*S**,7*S**,8*S**)-2,8-Dimethyltricyclo[5.3.0.0^{2,5}]decan-6-one (*rac*-64)**



***rac*-61**



***rac*-64**

Enone ***rac*-61** (37 mg, 0.25 mmol) was dissolved in DCM (25 mL) that had been presaturated with ethylene (C. P. grade) at −78 °C. The resulting solution was irradiated (−78 °C, 12 h) through a Pyrex filter (λ > 290 nm) using a 450-W Hanovia medium pressure mercury arc lamp. Ethene was bubbled through the stirred solution during the irradiation. The solution was concentrated by fractional distillation and the residual oil was purified by flash chromatography (2 g of silica gel, 4:1 pentane−Et_2O) to provide ketone ***rac*-64** as a colourless oil; yield: 40 mg (90%).

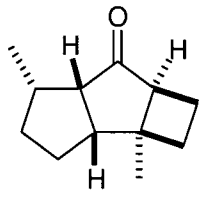
IR (film): ν = 2952, 1728, 1455, 1378, 1268 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.99 (d, 3 H, J = 7.3 Hz), 1.04-1.14 (m, 1 H), 1.23 (s, 3 H), 1.47-1.63 (m, 2 H), 1.64-1.79 (m, 3 H), 1.82-1.91 (m, 1 H), 2.09-2.15 (m, 1 H), 2.23-2.37 (m, 3 H), 2.93 (dd, 1 H, J = 9, 9 Hz).

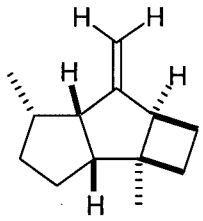
^{13}C NMR (100 MHz, APT): δ = 16.4 (−ve), 20.9 (+ve), 21.0 (−ve), 27.8 (+ve), 34.1 (+ve), 35.0 (+ve), 37.9 (−ve), 44.0 (+ve), 51.8 (−ve), 52.5 (−ve), 57.9 (−ve), 225.4.

Exact mass calculated for $C_{12}H_{18}O$: 178.1358; found 178.1361.

(1*R,2*S**,5*R**,7*S**,8*S**)-2,8-Dimethyl-6-methylidenetricyclo[5.3.0.0^{2,5}]decane (143)**



***rac*-64**



143

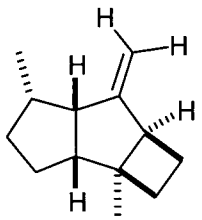
To a cold (0 °C) stirred suspension of Lombardo's reagent[85,86] (~ 1.4 mmol) in THF (4 mL) was added, sequentially, DCM (10 mL) and, via a cannula, a solution of ketone ***rac*-64** (128 mg, 0.72 mmol) in DCM (2 mL). The mixture was allowed to warm to r.t. and then was stirred for 16 h. Sat. aq. $NaHCO_3$ (10 mL) was added and the resulting biphasic mixture was filtered through a pad of neutral alumina (10 g). The alumina was eluted with Et_2O (20 mL). The phases of the combined eluate were separated and the organic phase was washed (brine, 10 mL), dried ($MgSO_4$), and concentrated by fractional distillation. Purification of the crude oil by flash chromatography (10 g of silica gel, pentane) provided alkene **143** as a colourless oil; yield: 81 mg (63%).

^{1}H NMR (400 MHz): δ = 0.89 (d, 3 H, J = 6.4 Hz), 1.14 (s, 3 H), 1.20-1.30 (m, 1 H), 1.32-1.43 (m, 1 H), 1.45-1.52 (m, 1 H), 1.53-1.63 (m, 3 H), 1.84 (dd, 1 H, J = 19,6, 9.1 Hz), 2.00-2.12 (m, 1 H), 2.18 (ddd, 1 H, J = 9, 9, 4.1 Hz), 2.23-2.36 (m, 2 H), 3.21-3.28 (m, 1H), 4.90-4.95 (m, 2 H).

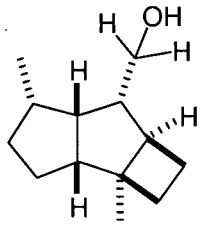
^{13}C NMR (75 MHz, APT): δ = 16.7 (−ve), 20.6 (−ve), 25.6 (+ve), 27.9 (+ve), 29.7 (+ve), 34.6 (+ve), 34.7 (+ve), 38.2 (−ve), 51.0 (−ve), 54.1 (−ve), 55.7 (−ve), 108.8 (+ve), 115.4.

Exact mass calculated for $C_{13}H_{20}$: 176.1565; found 176.1568.

(1*R,2*S**,5*R**,6*S**,7*S**,8*S**)-2,8-Dimethyl-6-(hydroxymethyl)tricyclo[5.3.0.0^{2,5}] decane (144)**



143



144

To a cold (0 °C) stirred solution of BH_3•THF (0.18 M in THF, 11 mL, 2 mmol) was added, via a cannula, a cold (0 °C) solution of alkene **143** (78 mg, 0.4 mmol) in pentane (3 mL). The solution was stirred at 0 °C for 3 h and then was treated with H_2O (110 μL, 6 mmol), aq NaOH (3 M, 3.3 mL, 10 mmol) and aq H_2O_2 (8.8 M, 1.2 mL, 10 mmol). The mixture was stirred overnight. The phases were separated and the organic phase was washed (brine, 10 mL), dried ($MgSO_4$) and concentrated. Chromatographic purification of the residual oil (8 g of silica gel, 9:1 pentane–Et_2O) provided alcohol **144** as a colourless oil; yield: 68 mg (80%).

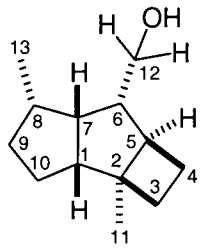
IR (film): ν = 3324, 2952, 1456, 1375, 1029 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.02 (d, 3 H, J = 7.2 Hz), 1.10-1.20 (m, 1 H), 1.16 (s, 3 H), 1.34 (dddd, 1 H, J = 14.0, 10.7, 9.1, 6.7 Hz), 1.38-1.46 (dddd, 1 H, J = 11.7, 8, 8, 3.8), 1.59 (dddd, 1 H, J = 14.0, 9.7, 9.7, 4.4 Hz), 1.70-1.77 (m, 1 H), 1.78 (dd, 2 H, J = 8, 8 Hz), 1.98-2.04 (dddd, 1 H, J = 10.2, 7.3, 4.6, 3.1), 2.07-2.16 (m, 2 H), 2.21-2.32 (m, 2 H), 2.88 (dd, 1H, J = 7.3, 7.3, 7.3 Hz), 3.33 (dd, 1 H, J = 10.2, 10.2 Hz), 3.93 (dd, 1 H, J = 10.2, 4.6 Hz). The hydroxyl proton was not observed in this spectrum.

^{13}C NMR (125 MHz): δ = 16.3, 20.4, 23.2, 26.5, 34.3, 35.0, 36.5, 46.8, 50.2, 52.3, 53.5, 57.0, 64.7.

Exact mass calculated for $C_{13}H_{22}O$: 194.1671; found 194.1664.

Table 4.3. NMR data for (1*R**,2*S**,5*R**,6*S**,7*S**,8*S**)-2,8-dimethyl-6-(hydroxymethyl)tricyclo[5.3.0.0^{2,5}]decane (**144**)



Carbon No.	^{13}C δ (ppm)[a]	1H δ (ppm)(mult; *J* (Hz))[b,c,d]	HMBC Correlations[e]
1	57.0	H-1: part of the m at 2.07-2.16 (m)	H-7, H-3α, H-3β, H-11
2	46.8		H-3α, H-3β, H-11
3	35.0	H-3α: 1.78 (dd; 8, 8)	H-11
		H-3β: 1.78 (dd; 8, 8)	
4	20.4	H-4α: part of the m at 2.07-2.16 (m)	H-3α, H-3β,
		H-4β; 1.38-1.46 (dddd; 11.7, 8, 8, 3.8)	
5	50.2	H-5: part of the m at 2.21-2.32 (m)	H-3α, H-3β, H-12a, H-12b
6	52.3	H-6: 1.98-2.04 (dddd; 10.2, 7.3, 4.6, 3.1)	H-7, H-8, H-12a, H-12b
7	53.5	H-7: 2.88 (ddd; 7.3, 7.3, 7.3)	H-13
8	36.5	H-8: part of the m at 2.21-2.32 (m)	H-7, H-13
9	34.2	H-9a; 1.10-1.20 (m)	H-7, H-13
		H-9b: 1.70-1.77 (m)	
10	26.5	H-10α: 1.34 (dddd; 14, 10.7, 9.1, 6.7)	H-7
		H-10β; 1.59 (dddd; 14, 9.7, 9.7, 4.4)	
11	23.2	H-11: 1.16 (s)	H-3α, H-3β,
12	64.7	H-12a: 3.33 (dd; 10.2, 10.2)	H-7
		H-12b: 3.93 (dd; 10.2, 4.6)	
13	16.3	H-13: 1.02 (d; 7.2)	H-7

[a] Recorded at 125 MHz.

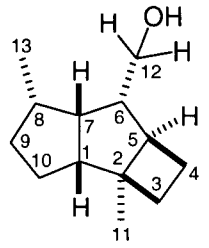
[b] Recorded at 500 MHz.

[c] Assignments based on HMQC data recorded at 500 MHz.

[d] Methylene protons are designated H-Xα if they are known to reside below the plane of the paper in the structure depicted above. They are designated H-Xβ if they are known to reside above the plane of the paper in the structure depicted above. If no information regarding their position relative to the plane of the paper is available then they are arbitrarily designated H-Xa and H-Xb.

[e] Only those correlations which could be unambiguously assigned are recorded.

Table 4.4. NMR data for (1*R**,2*S**,5*R**,6*S**,7*S**,8*S**)-2,8-dimethyl-6-(hydroxymethyl)tricyclo[5.3.0.0^{2,5}]decane (**144**)



Proton No.	1H δ (ppm)(mult; *J* (Hz))[a,b]	COSY Correlations[a,d]	NOE Correlations[d,e]
H-1	H-1: part of the m at 2.07-2.16 (m)	H-7, H-10α, H-10β	
H-3α	H-3α: 1.78 (dd; 8, 8)	H-4α, H-4β	
H-3β	H-3β: 1.78 (dd; 8, 8)	H-4α, H-4β	
H-4α	H-4α: part of the m at 2.07-2.16 (m)	H-3α, H-3β, H-4β, H-5	
H-4β	H-4β: 1.38-1.46 (dddd; 11.7, 8, 8, 3.8)	H-3α, H-3β, H-4α	
H-5	H-5: part of the m at 2.21-2.32 (m)	H-4α	
H-6	H-6: 1.98-2.04 (dddd; 10.2, 7.3, 4.6, 3.1)	H-7, H-12a, H-12b	H-3β, H-4β, H-7, H-8, H-12a, H-12b
H-7	H-7: 2.88 (ddd; 7.3, 7.3, 7.3)	H-1, H-6, H-8	H-1, H-4β, H-6, H-8, H-10β
H-8	H-8: part of the m at 2.21-2.32 (m)	H-7, H-13	
H-9a	H-9a: 1.10-1.20 (m)	H-9b, H-10α, H-10β	
H-9b	H-9b: 1.70-1.77 (m)	H-9a, H-10α, H-10β	
H-10α	H-10α: 1.34 (dddd; 14, 10.7, 9.1, 6.7)	H-1, H-9a, H-9b, H-10β	
H-10β	H-10β: 1.59 (dddd; 14, 9.7, 9.7, 4.4)	H-1, H-9a, H-9b, H-10α	
H-11	H-11: 1.16 (s)		
H-12a	H-12a: 3.33 (dd; 10.2, 10.2)	H-6, H-12b	H-5, H-6, H-10α, H-11, H-12b, H-13
H-12b	H-12b: 3.93 (dd; 10.2, 4.6)	H-6, H-12a	H-6, H-11, H-13, H-12a
H-13	H-13: 1.02 (d; 7.2)	H-8	

[a] Recorded at 500 MHz.

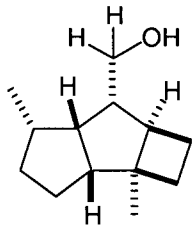
[b] Assignments based on HMQC data recorded at 500 MHz.

[c] Methylene protons are designated H-Xα if they are known to reside below the plane of the paper in the structure depicted above. They are designated H-Xβ if they are known to reside above the plane of the paper in the structure depicted above. If no information regarding their position relative to the plane of the paper is available then they are arbitrarily designated H-Xa and H-Xb.

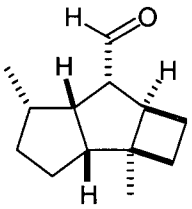
[d] Only those correlations which could be unambiguously assigned are recorded.

[e] Recorded as NOE difference at 500 MHz using 1D selective NOE difference experiments.

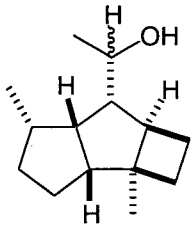
(1*R,2*S**,5*R**,6*S**,7*S**,8*S**)-6-Acetyl-2,8-dimethyltricyclo[5.3.0.0^{2,5}]decane (*rac*-81)**



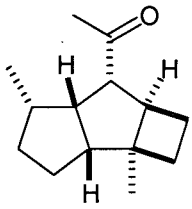
144



***rac*-80**



149



***rac*-81**

To a solution of alcohol **144** (20 mg, 0.10 mmol) in DCM (10 mL) was added TPAP (54 mg, 0.155 mmol) in one portion. The solution was stirred at r.t. for 30 min and then was filtered through a pad of silica gel (1 g) and the silica gel was eluted with Et_2O (20 mL). The filtrate was concentrated and the crude aldehyde (**rac-80**) was dissolved in Et_2O (10 mL). The solution was cooled (0 °C), treated with MeLi (1.6 M solution in Et_2O, 0.128 mL, 0.21 mmol), and allowed to warm up to r.t. over a period of 30 min. The mixture was treated with HOAc (11 μL, 0.21 mmol) and H_2O (5 mL). The phases were separated and the organic phase was washed (brine, 5 mL), dried ($MgSO_4$), and concentrated. The acquired crude mixture of diastereomeric secondary alcohols (**149**) was dissolved in DCM (10 mL). The solution was treated with TPAP (54 mg, 0.155 mmol) and then was stirred at r.t. for 30 min. The mixture was filtered through a pad of silica gel (1 g) and the silica gel was eluted with Et_2O (20 mL). The filtrate was concentrated and the crude oil was purified by flash column chromatography (1 g silica gel, 20:1 pentane–Et_2O) to provide ketone ***rac*-81** as a colourless oil; yield: 18 mg (86%).

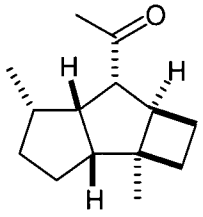
IR (film): ν = 2946, 1707, 1459, 1353, 1234, 1184 cm^{-1}.

^{1}H NMR (500 MHz): δ = 0.56 (d, 3 H, J = 7.3 Hz), 1.16 (s, 3 H), 1.27-1.38 (m, 2 H), 1.48-1.63 (m, 3 H), 1.73-1.80 (m, 1 H), 1.85-1.92 (m, 1 H), 2.19 (s, 3 H), 2.14-2.24 (m, 2 H), 2.31-2.41 (m, 2 H), 3.04-3.13 (m, 2 H).

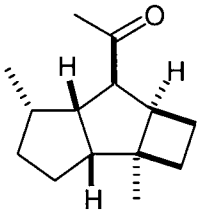
^{13}C NMR (100 MHz, APT): δ = 16.1 (+ve), 21.1 (+ve), 22.3 (−ve), 25.4 (−ve), 29.7 (+ve), 35.7 (+ve), 35.8 (−ve), 36.5 (−ve), 47.7 (−ve), 48.4 (+ve), 55.0 (+ve), 55.1 (+ve), 62.8 (+ve), 210.0 (−ve).

Exact mass calculated for $C_{14}H_{22}O$: 206.1671; found 206.1666.

(1*R,2*S**,5*R**,6*R**,7*S**,8*S**)-6-Acetyl-2,8-dimethyltricyclo[5.3.0.0^{2,5}]decane (*rac*-70)**



***rac*-81**



***rac*-70**

To a solution of ketone ***rac*-81** (18 mg, 0.08 mmol) in $CDCl_3$ (3 mL) was added 35% aq $HClO_4$ (1 mL) and the resulting biphasic mixture was heated to reflux for 20 h. The reaction mixture was cooled to r.t. and the phases were separated. The organic phase was washed (brine, 3 mL), dried ($MgSO_4$), and concentrated. Chromatography (1 g of silica gel, 20:1 pentane–Et_2O) of the crude oil provided ketone ***rac*-70** as a colourless oil; yield: 17 mg (95%).

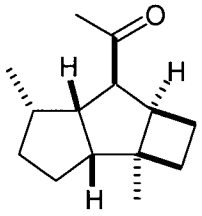
IR (film): ν = 2948, 1709, 1452, 1373, 1352, 1155 cm^{-1}.

^{1}H NMR (500 MHz): δ = 0.75 (d, 3 H, J = 6.9 Hz), 1.15 (s, 3 H), 1.18-1.27 (m, 1 H), 1.27-1.35 (m, 1 H), 1.35-1.42 (m, 1 H), 1.46-1.57 (m, 1H), 1.63-1.81 (m, 3 H), 1.81-1.95 (m, 1 H), 2.02 (s, 3 H), 2.05-2.14 (m, 1 H), 2.16-2.29 (m, 1 H), 2.61 (ddd, 1 H, J = 10.7, 6, 6 Hz), 2.89 (dd, 1 H, J = 10.7, 8.1 Hz), 3.21 (ddd, 1 H, J = 8, 7, 3.8 Hz).

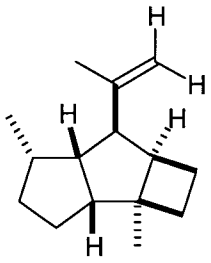
^{13}C NMR (100 MHz): δ = 15.3 (–ve), 17.4 (+ve), 23.2 (+ve), 26.0 (–ve), 30.0 (+ve), 32.4 (–ve), 33.0 (–ve), 35.8 (+ve), 47.1 (+ve), 47.6 (–ve), 49.8 (+ve), 55.3 (+ve), 56.8 (+ve), 208.7.

Exact mass calculated for $C_{14}H_{22}O$: 206.1671; found 206.1663.

(1*R,2*S**,5*R**,6*R**,7*S**,8*S**)-6-Isopropenyl-2,8-dimethyltricyclo[5.3.0.0^{2,5}]decane [(±)-kelsoene] (*rac*-35)**



***rac*-70**



***rac*-35**

To a cold (0 °C), stirred suspension of Lombardo's reagent[85,86] in THF (1 mL, ~0.35 mmol) was added, sequentially, DCM (5 mL) and, via a cannula, a solution of ketone ***rac*-70** (11 mg, 0.05 mmol) in DCM (2 mL). The mixture was allowed to warm up to r.t. and then was stirred for 6 h. Sat. aq $NaHCO_3$ (3 mL) was added and the resulting biphasic mixture was filtered through a pad of neutral alumina (1 g). The alumina was eluted with Et_2O (10 mL). The phases of the combined eluate were separated and the organic phase was washed (brine, 5 mL), dried ($MgSO_4$), and concentrated. Purification of the crude oil by chromatography (1 g of silica gel, pentane) provided (±)-kelsoene (***rac*-35**) as a colourless oil; yield: 9 mg (85%).

IR (film): ν = 3083, 2948, 2869, 1647, 1452, 1374, 886 cm^{-1}.

^{1}H NMR (500 MHz): δ = 0.89 (d, 3 H, J = 7.0 Hz), 1.14 (s, 3 H), 1.24-1.40 (m, 2 H), 1.43-1.54 (m, 2 H), 1.59 (s, 3 H), 1.61-1.69 (m, 2 H), 1.69-1.81 (m, 2 H), 2.06 (ddd, 1 H, J = 9, 9, 6.8 Hz), 2.24 (m, 1 H), 2.31-2.41 (m, 2 H), 2.84 (ddd, 1 H, J = 10.4, 7. 7 Hz), 4.77 (s, 1 H), 4.84 (s, 1 H).

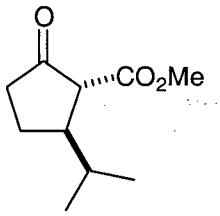
^{13}C NMR (100 MHz, APT): δ = 14.6 (−ve), 17.7 (+ve), 23.5 (+ve), 24.1 (+ve), 26.0 (−ve), 33.1 (−ve), 33.3 (−ve), 36.3 (+ve), 45.8, 47.5 (+ve), 48.1 (+ve), 50.0 (+ve), 57.8 (+ve), 109.8 (−ve), 145.6.

Exact mass calculated for $C_{15}H_{24}$: 204.1878; found 204.1870.

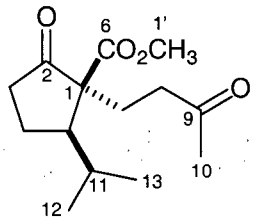
4.3 Experimental – Synthetic Approaches to (±)-Isomulinic Acid

Methyl (1*S,5*R**)-5-isopropyl-2-oxo-1-(3-oxobutyl)cyclopentane-1-carboxylate (199) and**

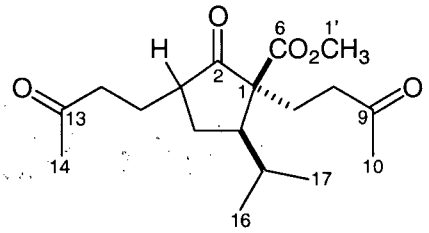
Methyl (1*S,3*S**,5*R**)-5-isopropyl-2-oxo-1,3-bis(3-oxobutyl)cyclopentane-1-carboxylate (200)**



198



199



200

Compound **199** was prepared using the method developed by Christoffers.[116] Thus, to a stirred mixture of neat keto ester **198** (30.0 g, 162 mmol) and freshly distilled methyl vinyl ketone (12.5 g, 178 mmol) was added a catalytic amount of $FeCl_3 \bullet 6H_2O$ (440 mg, 1.6 mmol). Upon addition of $FeCl_3 \bullet 6H_2O$ the mixture turned deep purple in colour. The mixture was allowed to stir under an atmosphere of air. After 2 days, the mixture was filtered through a pad of silica gel and the silica gel was rinsed with Et_2O. The eluate was concentrated and the crude material was purified by flash column chromatography (700 g of silica gel, 3:1 petroleum ether-Et_2O) to yield compound **199** as a clear oil (25.8 g, 63%). Keto ester **198** (5.5 g, 18%) and trione **200** (2.6 g, 5%) were also isolated as clear oils from the crude mixture.

Compound **199** exhibited:

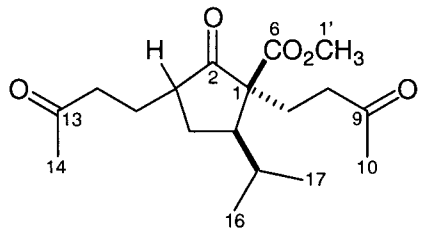
IR (film): ν = 2958, 1749, 1731, 1718, 1439, 1360, 1229, 1162 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.82 (d, 3 H, J = 6.6 Hz, Me-12 or Me-13), 0.91 (d, 3 H, J = 6.6 Hz, Me-12 or Me-13), 1.45-1.58 (m, 1 H, H-11), 1.67-1.86 (m, 2 H), 1.89-1.99 (ddd, 1 H, J = 14.4, 9.5, 4.7 Hz), 2.01-2.22 (m, 2 H), 2.08 (s, 3 H, Me-10), 2.26-2.50 (m, 3 H), 2.61-2.72 (ddd, 1 H, J = 17.3, 10.0, 5.9 Hz), 3.63 (s, 3 H, Me-1').

^{13}C NMR (100 MHz): δ = 20.9, 22.2, 24.9, 28.0, 29.8, 30.5, 38.6, 38.6, 51.8, 53.4, 61.5 (C-1), 171.0 (C-6), 207.9 (C-9), 216.5 (C-2).

Exact mass calculated for $C_{14}H_{22}O_4$: 254.1518; found 254.1518.

Compound **200** exhibited:



200

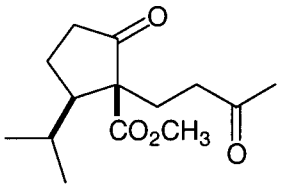
IR (film): ν = 2956, 1747, 1730, 1716, 1225, 1161 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.86 (d, 3 H, J = 6.6 Hz, Me-16 or Me-17), 0.94 (d, 3 H, J = 6.6 Hz, Me-16 or Me-17), 1.30-1.40 (m, 1 H), 1.44-1.54 (m, 1 H), 1.61-1.73 (dddd, 1 H, J = 11.8, 11.8, 11.8, 7.6 Hz), 1.75-1.91 (m, 2 H), 2.00-2.06 (dd, 1 H, J = 14.4, 1.6 Hz), 1.99-2.10 (m, 1 H), 2.11-2.26 (m, 2 H), 2.13 (s, 3 H, Me-10 or Me-14), 2.17 (s, 3 H, Me-10 or Me-14), 2.32-2.49 (m, 2 H), 2.56-2.68 (ddd, 1 H, J = 18.2, 7.5, 7.5 Hz), 2.67-2.74 (m, 1 H), 3.62 (s, 3 H, Me-1').

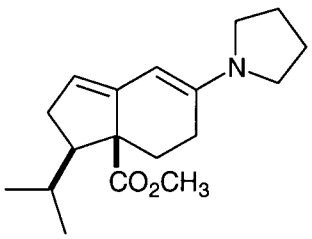
^{13}C NMR (100 MHz): δ = 20.7, 22.2, 25.1, 25.9, 28.7, 29.9, 30.2, 34.7, 38.8, 39.8, 47.2, 51.7, 55.2, 61.4 (C-1), 171.4 (C-6), 207.8 (C-9 or C-13), 210.7 (C-9 or C-13), 216.6 (C-2).

Exact mass calculated for $C_{18}H_{28}O_5$: 324.1937; found 324.1939.

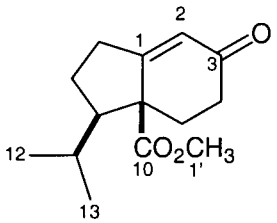
Methyl (6*S,7*R**)-7-isopropyl-3-oxobicyclo[4.3.0]non-1-ene-6-carboxylate (197)**



199



207



197

Enone **197** was prepared using the method described by Scanio and Hill.[118] Thus, a 500 mL round-bottom flask equipped with a Dean-Stark water separator and a condenser was charged with a solution of diketone **199** (25.8 g, 102 mmol) and pyrrolidine (14.5 g, 204 mmol) in benzene (250 mL). The mixture was stirred and heated to reflux for 3 h under an atmosphere of argon. After that time the mixture was concentrated to provide the crude dienamine **207** as a brown oil.

A 250 mL round-bottom flask equipped with a condenser was charged with a benzene (70 mL) solution of crude dienamine **207**. A solution of sodium acetate (1.9 g, 23 mmol) and glacial acetic acid (3.8 mL) in water (3.8 mL) was then added and the resulting biphasic mixture was heated to reflux for 4 h. After this time the mixture was washed successively with water (100 mL), 10% aq. HCl (100 mL), sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$) and concentrated to provide crude enone **197** as a yellow oil which crystallized on standing. The crude material was recrystallized from hot DCM to furnish 18.1 g (76%) of pure enone **197** which exhibited:

m.p. = 83-84 °C

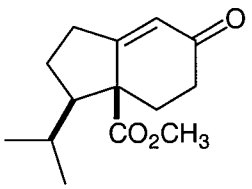
IR (film): ν = 2967, 1721, 1664, 1333, 1229, 1168 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.88 (d, 3 H, J = 6.4 Hz, Me-12 or Me-13), 1.03 (d, 3 H, J = 6.4 Hz, Me-12 or Me-13), 1.44-1.62 (m, 2 H), 1.63-1.79 (m, 2 H), 1.95-2.05 (m, 1 H), 2.28-2.37 (ddd, 1 H, J = 16.1, 4.3, 1.8 Hz), 2.37-2.43 (dd, 1 H, J = 13.6, 4.6 Hz), 2.43-2.55 (m, 1 H), 2.78-2.89 (dddd, 1 H, 19.6, 11.0, 2.2, 2.2 Hz), 2.86-2.93 (ddd, 1 H, J = 13.1, 4.6, 2.5 Hz), 3.68 (s, 3 H, Me-1'), 5.81 (s, 1 H, H-2).

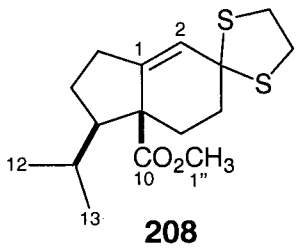
^{13}C NMR (100 MHz): δ = 22.1, 22.4, 27.6, 30.6, 30.9, 34.1, 34.7, 52.0, 56.8, 58.5, 123.4 (C-2), 171.2 (C-1 or C10), 172.3 (C-1 or C-10), 198.8 (C-3).

Exact mass calculated for $C_{14}H_{20}O_3$: 236.1412; found 236.1412.

Methyl (6*S,7*R**)-7-isopropyl-3-oxobicyclo[4.3.0]non-1-ene-6-carboxylate-3,3-ethylenedithioketal (208)**



197



208

To a stirred solution of enone **197** (20.4 g, 86.4 mmol) in DCM (280 mL) under an atmosphere of argon were added, sequentially, 1,2-ethanedithiol (24.4 g, 21.7 mL, 105 mmol) and neat $BF_3 \bullet Et_2O$ (1.23 g, 1.10 mL, 8.64 mmol). The resulting mixture was allowed to stir for 36 h. The mixture was then diluted with Et_2O (250 mL), washed successively with tris(hydroxy-methyl)aminomethane buffer (pH = 8, 0.5 M, 250 mL) and brine (250 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash chromatography (500 g of silica gel, 19:1 petroleum ether-Et_2O) to yield 25.0 g (93%) of dithioketal **208** as a clear oil.

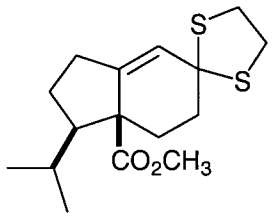
IR (film): ν = 2948, 1718, 1436, 1169, 739 cm^{-1}.

^1H NMR (400 MHz): δ = 0.81 (d, 3 H, J = 6.2 Hz, Me-12 or Me-13), 0.97 (d, 3 H, J = 6.2 Hz, Me-12 or Me-13), 1.32-1.59 (m, 4 H), 1.81-1.91 (m, 1 H), 1.98-2.08 (ddd, 1 H, J = 13.7, 13.7, 2.5 Hz), 2.18-2.29 (m, 2 H), 2.57-2.68 (m, 1 H), 2.69-2.78 (ddd, 1 H, 13.2, 4.2, 2.6 Hz), 3.12-3.20 (m, 1 H), 3.25-3.40 (m, 3 H), 3.62 (s, 3 H, Me-1"), 5.51-5.55 (ddd, 1 H, J = 1.5, 1.5, 1.5 Hz, H-2).

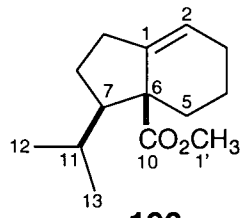
^{13}C NMR (100 MHz): δ = 22.2 (−ve, C-12 or C-13), 22.3 (−ve, C-12 or C-13), 27.6 (+ve), 29.5 (+ve), 31.3 (−ve), 34.1 (+ve), 39.4 (+ve), 40.1 (+ve), 40.3 (+ve), 51.4 (−ve), 55.4 (+ve), 58.6 (−ve), 65.3 (+ve), 125.0 (−ve, C-2), 145.5 (+ve, C-1), 173.6 (+ve, C-10).

Exact mass calculated for $C_{16}H_{24}O_2S_2$: 312.1218; found: 312.1216.

Methyl (6*S,7*R**)-7-isopropylbicyclo[4.3.0]non-1-ene-6-carboxylate (196)**



208



196

A 500 mL round bottom flask equipped with an overhead mechanical stirrer was charged with a solution of dithioketal **208** (25.0 g, 80.1 mmol) in EtOH (200 mL). Excess Raney nickel (W-2, 50% in H_2O, 150 g) was added in portions over a span of 2 days until no starting material could be detected by TLC analysis. 10% aq. HCl (50 mL) was added and the reaction mixture was stirred overnight. The mixture was filtered through a pad of Celite® and the remaining solid was rinsed with petroleum ether until no product was detected in the eluate by TLC analysis. The phases of the eluate were allowed to separate and the petroleum ether phase was washed with brine (2 x 200 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (300 g of silica gel, 19:1 petroleum ether-Et_2O) to yield 10.3 g (66%) of alkene **196** as a clear oil.

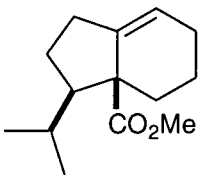
IR (film): ν = 2948, 1724, 1433, 1164, 1008, 795 cm^{-1}.

^1H NMR (400 MHz): δ = 0.84 (d, 3 H, J = 6.4 Hz, Me-12 or Me-13), 0.98-1.06 (m, 1 H, H-5α), 1.01 (d, 3 H, J = 6.3 Hz, Me-12 or Me-13), 1.30-1.59 (m, 4 H), 1.64-1.75 (m, 1 H), 1.79-1.89 (m, 1 H), 1.91-2.04 (m, 2 H), 2.17-2.29 (m, 1 H), 2.56-2.68 (m, 1 H), 2.68-2.74 (ddd, 1 H, J = 12.6, 3.6, 3.1 Hz, H-5β), 3.63 (s, 3 H, Me-1'), 5.44 (br. s, 1 H, H-2).

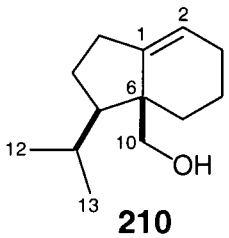
^{13}C NMR (100 MHz): δ = 20.1 (+ve), 22.2 (−ve, C-12 or C-13), 22.6 (−ve, C-12 or C-13), 24.7 (+ve), 27.3 (+ve), 29.7 (+ve), 31.3 (−ve, C-7 or C-11), 33.4 (+ve), 51.2 (−ve, C-7 or C-11), 55.4 (+ve, C-6), 59.1 (−ve, C-1'), 120.5 (−ve, C-2), 143.8 (+ve, C-1), 174.9 (+ve, C-10).

Exact mass calculated for $C_{14}H_{22}O_2$: 222.1620; found: 222.1622.

(6*S,7*R**)-6-hydroxymethyl-7-isopropylbicyclo[4.3.0]non-1-ene (210)**



196



210

To a cold (0 °C), stirred solution of ester **196** (3.16 g, 14.2 mmol) in Et_2O (100 mL) was added a solution of DIBAL-H in hexanes (1.0 M, 31.3 mL, 31.3 mmol). The reaction mixture was stirred at this temperature until no starting material could be detected by TLC analysis. Excess $MgSO_4 \bullet 7H_2O$ (8.0 g, 32.5 mmol) was added and the resulting heterogeneous mixture was stirred vigorously for 1 h. The mixture was then filtered through a sintered glass funnel and the funnel was rinsed with Et_2O until no product could be detected in the eluate by TLC analysis. The collected eluate was concentrated and the residual oil was chromatographed (150 g of silica gel, 9:1 petroleum ether-Et_2O) to furnish alcohol **210** as a clear and colourless oil; yield: 2.35 g (85%).

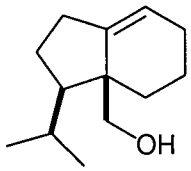
IR (film): ν = 3369, 2932, 1473, 1034 cm^{-1}.

^1H NMR (400 MHz): δ = 0.86 (d, 3 H, J = 6.6 Hz, Me-12 or Me-13), 0.99 (d, 3 H, J = 6.6 Hz, Me-12 or Me-13), 1.14-1.28 (m, 3 H), 1.34-1.47 (dddd, 1 H, J = 11.6, 11.6, 9.9, 6.7 Hz), 1.56-1.67 (m, 2 H), 1.77-1.91 (m, 2 H), 1.93-2.00 (m, 2 H), 2.11-2.20 (dddd, 1 H, 16.3, 8.3, 3.3, 1.6 Hz), 2.18-2.25 (ddd, 1 H, J = 13.1, 8, 8 Hz), 2.27-2.38 (m, 1 H), 3.54-3.59 (br. s, 2 H, H-10), 5.54-5.59 (m, 1 H, H-2).

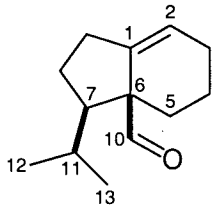
^{13}C NMR (100 MHz): δ = 19.2 (+ve), 23.1 (−ve, C-12), 23.1 (−ve, C-13), 24.5 (+ve), 27.3 (+ve), 28.3 (+ve), 30.2 (−ve), 34.7 (+ve), 48.0 (+ve, C-6), 58.3 (−ve), 64.9 (+ve, C-10), 121.9 (−ve, C-2), 144.0 (+ve, C-1).

Exact mass calculated for $C_{13}H_{22}O$: 194.1671; found: 194.1676.

(6*S,7*R**)-7-Isopropylbicyclo[4.3.0]non-1-ene-6-carbaldehyde (211)**



210



211

Alcohol **210** was oxidized to aldehyde **211** using the method developed by Ley.[88] Thus, to a solution of alcohol **210** (6.82 g, 35.2 mmol) in DCM (250 mL) were added, sequentially, NMO (4.94 g, 42.2 mmol) in one portion and TPAP (475 mg, 1.4 mmol) in one portion. The resulting mixture was stirred overnight under an atmosphere of argon. TLC analysis of the mixture indicated that most of the starting material had been consumed. The reaction mixture was filtered through a pad of silica gel and the silica gel was rinsed with Et_2O. The eluate was concentrated and the residual oil was purified by flash chromatography (350 g of silica gel, 19:1 petroleum ether-Et_2O) to furnish aldehyde **211** as a colourless oil; yield: 6.12 g (91%).

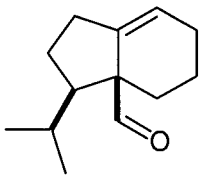
IR (film): ν = 2942, 1718, 1472, 1368, 880 cm^{-1}.

^1H NMR (400 MHz): δ = 0.86 (d, 3 H, J = 6.6 Hz, Me-12 or Me-13), 0.96 (d, 3 H, J = 6.6 Hz, Me-12 or Me-13), 1.02-1.11 (ddd, 1 H, J = 13.7, 13.7, 3.2 Hz, H-5α), 1.32-1.46 (m, 2 H), 1.49-1.46 (dddd, 1 H, J = 13.0, 11.5, 11.5, 7.0 Hz), 1.58-1.72 (m, 2 H), 1.89-1.96 (m, 2 H), 1.94-2.04 (dddd, 1 H, J = 13.3, 9.8, 8.2, 3.8 Hz), 2.29-2.40 (m, 1 H), 2.52-2.63 (m, 1 H), 2.58-2.66 (ddd, 1 H, J = 13.0, 3.5, 3.5 Hz, H-5β), 5.56-5.62 (m, 1 H, H-2), 9.65 (s, 1 H, H-10).

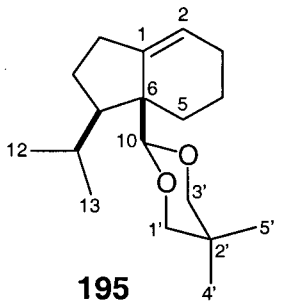
^{13}C NMR (100 MHz): δ = 19.9 (+ve), 22.5 (−ve, C-12 or C-13), 22.6 (−ve, C-12 or C-13), 24.5 (+ve), 27.5 (+ve), 28.8 (+ve), 30.3 (+ve), 30.7 (−ve, C-7 or C-11), 59.0 (−ve, C-7 or C-11), 60.0 (+ve, C-6), 122.7 (−ve, C-2), 141.1 (+ve, C-1), 203.2 (−ve, C-10).

Exact mass calculated for $C_{13}H_{20}O$: 192.1514; found 192.1515.

(6*S,7*R**)-7-Isopropylbicyclo[4.3.0]non-1-ene-6-carbaldehyde 2',2'-dimethylpropylene acetal (195)**



211



195

To a solution of aldehyde **211** (6.12 g, 22.0 mmol) in DCM (250 mL) at r.t. was added 2,2-dimethyl-1,3-propanediol (22.9 g, 220 mmol). A catalytic amount of *p*-TSA•H_2O (210 mg, 1.1 mmol) was added and the reaction mixture was allowed to stir overnight. TLC analysis of the reaction mixture indicated that the starting material had been consumed. The mixture was diluted with Et_2O (30 mL), washed successively with water (2 x 30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (450 g of silica gel, 49:1 petroleum ether-Et_2O) to furnish acetal **195** as a colourless oil; yield: 8.47 g (95%).

IR (film): ν = 2952, 1471, 1393, 1116, 1019 cm^{-1}.

^1H NMR (400 MHz): δ = 0.67 (s, 3 H, Me-4' or Me-5'), 0.83 (d, 3 H, *J* = 6.7 Hz, Me-12 or Me-13), 0.82-0.98 (m, 1 H, H-5α), 0.98 (d, 3 H, *J* = 6.4 Hz, Me-12 or Me-13), 1.05-1.14 (m, 1 H), 1.16 (s, 3 H, Me-4' or Me-5'), 1.38-1.51 (ddd, 1 H, *J* = 12, 12, 6.0 Hz), 1.52-1.60 (m, 1 H), 1.63-1.74 (dddd, 1 H, *J* = 13.1, 9,9, 6.5, 6.5 Hz), 1.76-1.87 (dddd, 1 H, 12.9, 9.9, 8.8, 4.3 Hz), 1.87-2.03 (m, 3 H), 2.08-2.17 (dddd, 1 H, *J* = 15.9, 8.8, 6.2, 1.2 Hz), 2.26-2.38 (m, 1 H), 2.57-2.64 (ddd, 1 H, *J* = 12.9, 3, 3 Hz, H-5β), 3.28 (d, 1 H, *J* = 10.7 Hz, H-1'ax or H-3'ax), 3.36 (d, 1 H, *J* = 10.7 Hz, H-1'ax or H-3'ax), 3.57-3.62 (dd, 1 H, *J* = 10.7, 2.9 Hz, H-1'eq or H-3'eq), 3.60-3.65 (dd, 1 H, *J* = 10.7, 2.9 Hz, H-1'eq, or H-3'eq), 4.33 (s, 1 H, H-10), 5.47 (d, 1 H, 1.5 Hz, H-2).

^{13}C NMR (100 MHz): δ = 19.8 (+ve), 21.8 (−ve), 23.0 (−ve), 23.2 (−ve), 23.2 (−ve), 24.8 (+ve), 27.6 (+ve), 28.8 (+ve), 30.0 (+ve, C-2'), 30.5 (−ve), 31.6 (+ve), 49.9 (+ve), 59.2 (−ve), 77.4 (+ve, C-1' or C-3'), 78.2 (+ve, C-1' or C-3'), 103.4 (−ve, C-10), 119.5 (−ve, C-2), 144.6 (+ve, C-1).

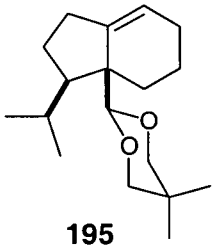
Exact mass calculated for $C_{18}H_{30}O_2$: 278.2246; found: 278.2247.

Hydroboration of alkene 195, preparation of

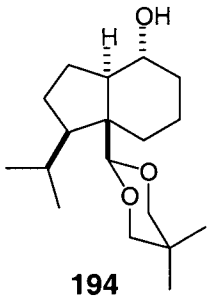
(1*S,5*R**,6*R**,9*R**)-5-Hydroxy-9-isopropylbicyclo[4.3.0]nonane-1-carbaldehyde-2',2'-dimethylpropylene acetal (194),**

(1*S,5*S**,6*S**,9*R**)-5-Hydroxy-9-isopropylbicyclo[4.3.0]nonane-1-carbaldehyde-2',2'-dimethylpropylene acetal (213) and**

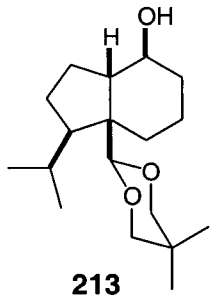
(1*S,5*S**,6*S**,9*R**)-1-(3'-hydroxy-2',2'-dimethylpropoxymethyl)-5-hydroxy-9-isopropylbicyclo[4.3.0]nonane (214)**



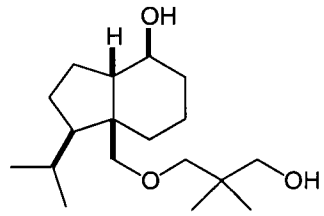
195



194



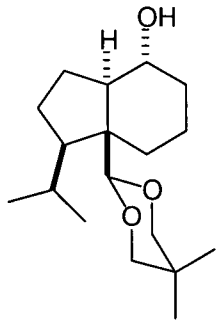
213



214

To a stirred solution of alkene **195** (262 mg, 0.94 mmol) in DCM (54 mL) was added, via a syringe, neat BH_3•SMe_2 (134 μL, 1.41 mmol, 1.5 equiv.). The resulting solution was stirred at room temperature for 24 h. TLC analysis of the solution indicated that all the starting material had been consumed. The reaction mixture was then treated with H_2O (1 mL, 55.6 mmol), aq NaOH (3 M, 2.83 mL, 8.5 mmol) and aq H_2O_2 (8.8 M, 0.96 mL, 8.5 mmol) and was allowed to stir overnight. Neat AcOH (0.49 mL, 8.5 mmol) was added. The phases were separated and the organic phase was washed with brine (30 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (25 g of silica gel, 1:1 petroleum ether-Et_2O) to yield a mixture of alcohols **194** and **213** (ratio 1.5:1, 219 mg, 0.74 mmol) as a clear oil and in 79% combined yield. This mixture of alcohols **194** and **213** proved difficult to separate. Elution of the baseline material with Et_2O provided diol **214** (53 mg, 0.18 mmol) as a clear oil in 19% yield.

(1*S,5*R**,6*R**,9*R**)-5-Hydroxy-9-isopropylbicyclo[4.3.0]nonane-1-carbaldehyde-2',2'-dimethylpropylene acetal (194)**

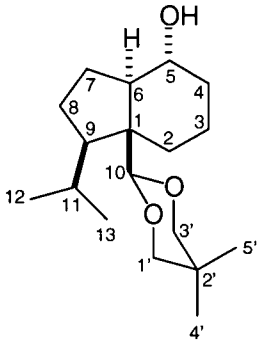


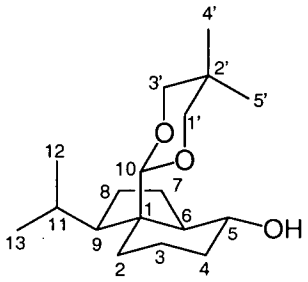
A small amount (30 mg) of alcohol **194** could be separated from the previously obtained mixture of alcohols **194** and **213** by flash column chromatography (25 g of silica gel, DCM). Alcohol **194** displayed:

^{1}H NMR (400 MHz): δ = 0.62 (s, 3 H), 0.74-0.83 (m, 1 H), 0.78 (d, 3 H, J = 6.7 Hz), 0.92 (d, 3 H, J = 6.7 Hz), 0.96-1.03 (m, 1 H), 1.02-1.10 (ddd, 1 H, J = 10, 10, 10 Hz), 1.12 (s, 3 H), 1.23-1.48 (m, 4 H), 1.51-1.62 (m, 2 H), 1.74-1.91 (m, 3 H), 1.96-2.04 (m, 1 H), 2.41-2.50 (ddd, 1 H, J = 13.0, 3.0, 3.0 Hz), 3.20-3.26 (ddd, 1 H, J = 10.2, 10.2, 5.0 Hz), 3.26-3.32 (d, 1 H, J = 11.2 Hz), 3.52-3.58 (d, 1 H, J = 11.2 Hz), 3.55-3.60 (dd, 1 H, J = 11.2, 2.7 Hz), 4.10-4.17 (dd, 1 H, J = 11.2, 2.7 Hz), 4.25 (s, 1 H).

^{13}C NMR (100 MHz): δ = 21.9 (−ve), 22.8 (−ve), 22.8 (+ve), 23.0 (+ve), 23.3 (−ve), 23.5 (−ve), 28.7 (+ve), 29.9 (+ve), 31.2 (−ve), 34.4 (+ve), 35.9 (+ve), 51.6 (+ve), 58.2 (−ve), 59.7 (−ve), 70.1 (−ve), 77.3 (+ve), 77.9 (+ve), 104.1 (−ve).

Table 4.5: NMR data for (1*S**,5*R**,6*R**,9*R**)-5-hydroxy-9-isopropylbicyclo[4.3.0]nonane-1-carbaldehyde-2',2,-dimethylpropylene acetal (**194**)





Carbon No.	^{13}C δ (ppm)[a]	^{1}H δ (ppm) (mult; *J* (Hz))[b,c,d]	HMBC Correlations[e]
1	51.6		H-2ax, H-2eq, H-9
2	34.4	H-2ax: 0.74-0.83 (m)	H-4ax, H-4eq, H-9, H-10
		H-2eq: 2.41-2.50 (ddd, *J* = 13.0, 3.0, 3.0)	
3	22.8	H-3eq: part of the m at 1.51-1.62	H-2ax, H-2eq, H-4eq
		H-3ax: part of the m at 1.74-1.91	
4	35.9	H-4ax: 0.96-1.03 (m)	H-5
		H-4eq: 1.96-2.04 (m)	
5	70.1	H-5: 4.10-4.17 (ddd, *J* = 10, 10, 5.0)	H-4ax, H-4eq
6	58.2	H-6: part of the m at 1.23-1.48	H-2ax, H-2eq, H-4ax, H-4eq, H-5
7	23.0	H-7a: see footnote f	H-2ax, H-2eq
		H-7b: see footnote f	
8	28.7	H-8a: part of the m at 1.23-1.48	H-9
		H-8b: part of the m at 1.74-1.91	
9	59.7	H-9: 1.02-1.10 (ddd, *J* = 10, 10, 10)	H-10, H-12, H-13
10	104.1	H-10: 4.25 (s)	H-2ax, H-2eq, H-1'ax, H-1'eq, H-3'ax, H-3'eq
11	31.2	H-11: part of the m at 1.51-1.62	H-9, H-12, H-13
12	23.3	H-12: 0.78 (d, *J* = 6.7)	H-13
13	22.8	H-13: 0.92 (d, *J* = 6.7)	H-12
1'	77.3	H-1'ax: 3.26-3.32 (d, *J* = 11.2)	H-10, H-3'ax, H-3'eq, H-4', H-5'
		H-1'eq: 3.51-3.56 (dd, *J* = 11.2, 2.7)	
2'	29.9		H-10, H-1'ax, H-1'eq, H-3'ax, H-3'eq, H-4', H-5'
3'	77.9	H-3'ax: 3.20-3.26 (d, *J* = 11.2)	H-10, H-1'ax, H-1'eq, H-4', H-5'
		H-3'eq: 3.55-3.60 (dd, *J* = 11.2, 2.7)	
4'	21.9	H-4': 0.62 (s)	H-1'ax, H-3'ax, H-5'
5'	23.5	H-5': 1.12 (s)	H-1'ax, H-1'eq, H-3'ax, H-3'eq, H-4'

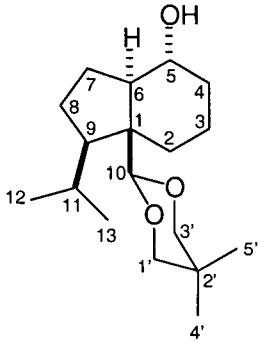
[a] Recorded at 100 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC and JMOD data.

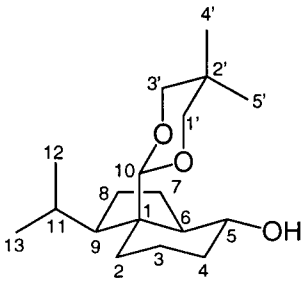
[d] Methylene protons are designated H-Xax and H-Xeq if they are known to occupy axial and equatorial positions, respectively, in the conformation depicted above. If no information regarding their relative position is known then they are designated H-Xa and H-Xb arbitrarily.

[e] Only those correlations which could be unambiguously assigned are recorded.

[f] One of the proton signals which occur at δ = 1.74-1.91 and two of the proton signals which occur at δ = 1.23-1.48 remain unassigned. They account for the methylene protons on C-7 and the hydroxyl group proton.

Table 4.6: NMR data for (1*S**,5*R**,6*R**,9*R**)-5-hydroxy-9-isopropylbicyclo[4.3.0]nonane-1-carbaldehyde-2',2,-dimethylpropylene acetal (**194**)





Proton No	^{1}H δ (ppm) (mult; *J* (Hz))[a,b,c]	COSY Correlations[d]	NOE Correlations[d,e]
H-2ax	0.74-0.83 (m)	H-2eq, H-3ax, H-3eq	
H-2eq	2.41-2.50 (ddd, *J* = 13.0, 3.0, 3.0)	H-2ax, H-3ax, H-3eq	H-2ax, H-3ax, H-3eq, H-10, H-13
H-3eq	part of the m at 1.51-1.62	H-2ax, H-2eq, H-4ax, H-4eq	
H-3ax	part of the m at 1.74-1.91	H-2ax, H-2eq, H-4ax, H-4eq	
H-4ax	0.96-1.03 (m)	H-3ax, H-3eq, H-4eq, H-5	
H-4eq	1.96-2.04 (m)	H-3ax, H-3eq, H-4ax, H-5	H-4ax, H-5
H-5	4.10-4.17 (ddd, *J* = 10, 10, 5.0)	H-4ax, H-4eq, H-6	H-3ax, H-4eq, H-10
H-6	part of the m at 1.23-1.48	H-6	
H-7a	see footnote f		
H-7b	see footnote f		
H-8a	part of the m at 1.23-1.48	H-9	
H-8b	part of the m at 1.74-1.91	H-9	
H-9	1.02-1.10 (ddd, *J* = 10, 10, 10)	H-8a, H-8b, H-11	
H-10	4.25 (s)		H-2eq, H-3ax, H-5, H-1'ax, H-3'ax
H-11	part of the m at 1.51-1.62	H-9, H-12, H-13	
H-12	0.78 (d, *J* = 6.7)	H-11	
H-13	0.92 (d, *J* = 6.7)	H-11	
H-1'ax	3.26-3.32 (d, *J* = 11.2)	H-1'eq	
H-1'eq	3.51-3.56 (dd, *J* = 11.2, 2.7)	H-1'ax, H-3'eq	
H-3'ax	3.20-3.26 (d, *J* = 11.2)	H-3'eq	
H-3'eq	3.55-3.60 (dd, *J* = 11.2, 2.7)	H-3'ax, H-1'eq[•]	
H-4'	0.62 (s)		
H-5'	1.12 (s)		

[a] Recorded at 400 MHz. [b] Assignments based on HMQC and JMOD data.

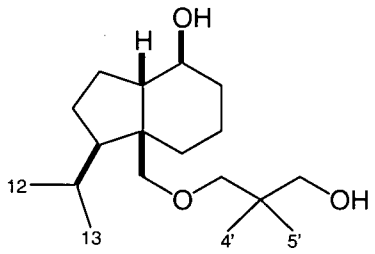
[c] Methylene protons are designated H-Xax and H-Xeq if they are known to occupy axial and equatorial positions, respectively, in the conformation depicted above. If no information regarding their relative position is known then they are designated H-Xa and H-Xb arbitrarily.

[d] Only those correlations which could be unambiguously assigned are recorded.

[e] Recorded as NOE difference at 400 MHz using 1D selective NOE experiments.

[f] One of the proton signals which occur at δ = 1.74-1.91 and two of the proton signals which occur at δ = 1.23-1.48 remain unassigned. They account for the methylene protons on C-7 and the hydroxyl group proton.

(1*S,5*S**,6*S**,9*R**)-1-(3'-Hydroxy-2',2'-dimethylpropoxymethyl)-5-hydroxy-9-isopropylbicyclo[4.3.0]nonane (214)**



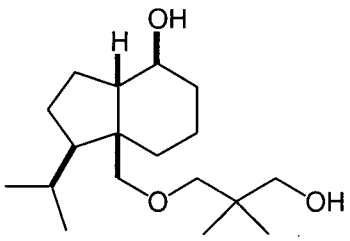
IR (film): ν = 3370, 2949, 1460, 1111, 1042, 739 cm^{-1}.

^1H NMR (400 MHz): δ = 0.80 (d, 3 H, J = 6.6 Hz, Me-12 or Me-13), 0.88 (d, 3 H, J = 6.5 Hz, Me-12 or Me-13), 1.20-1.37 (m, 1 H), 1.37-1.48 (m, 1 H), 1.55-1.68 (dddd, 1 H, J = 11.6, 11.6, 11.6, 7.6 Hz), 1.68-1.82 (m, 2 H), 1.92-2.20 (m, 7 H), 2.05 (s, 3 H, Me-4' or Me-5'), 2.09 (s, 3 H, Me-4' or Me-5'), 2.24-2.42 (m, 3 H), 2.49-2.60 (ddd, 1 H, J = 18.4, 7.5, 7.5 Hz), 2.59-2.66 (dddd, 1 H, J = 8.9, 8.9, 4.0, 1.9 Hz), 3.54-3.60 (m, 3 H). The hydroxyl protons were not observed in this spectrum.

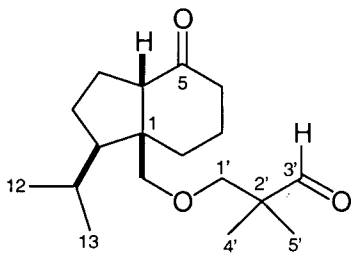
^{13}C NMR (100 MHz): δ = 19.0, 21.9, 21.9, 22.6, 23.5, 24.9, 27.0, 29.2, 29.8, 33.5, 36.3, 49.1, 49.4, 50.9, 71.0, 71.3, 75.4, 80.4.

Exact mass calculated for $C_{18}H_{35}O_3$ $[M+H]^+$: 299.2587; found 299.2587.

(1*S,6*S**,9*R**)-1-(2',2'-dimethyl-3-oxopropoxymethyl)-9-isopropyl-5-oxobicyclo-[4.3.0]nonane (215)**



214



215

Diol **214** was oxidized to the keto aldehyde **215** using the method developed by Ley.[88] Thus, to a stirred solution of diol **214** (53 mg, 0.18 mmol) in DCM (10 mL) at r.t. was added, sequentially, NMO (31 mg, 0.27 mmol) in one portion and TPAP (10 mg, 0.03 mmol) in one portion. The resulting mixture was stirred for 30 min. TLC analysis of the mixture indicated that the starting material had been consumed. The reaction mixture was filtered through a pad of silica gel (1 g) and the silica gel was rinsed with Et_2O. The collected eluate was concentrated and the residual oil was purified by flash column chromatography (5 g of silica gel, 1:1 petroleum ether-Et_2O) to afford keto aldehyde **215** as a colourless oil. Yield: 47 mg (90%).

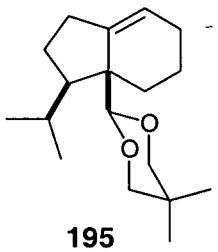
IR (film): ν = 2956, 2872, 1729, 1707, 1471, 1114, 738 cm^{-1}.

^1H NMR (400 MHz): δ = 0.78 (d, 3 H, J = 6.7 Hz, Me-12 or Me-13), 0.89 (d, 3 H, J = 6.3 Hz, Me-12 or Me-13), 1.03 (s, 6 H, Me-4' and Me-5'), 1.22-1.34 (m, 2 H), 1.46-1.62 (m, 3 H), 1.68-1.94 (m, 4 H), 1.98-2.09 (m, 1 H), 2.14-2.30 (m, 2 H), 2.61-2.65 (dd, 1 H, J = 8.3, 4.9 Hz), 3.23 (d, 1 H, J = 8.8 Hz), 3.29 (d, 1 H, J = 8.8 Hz), 3.24 (d, 1 H, J = 8.9 Hz), 3.40 (d, 1 H, J = 8.9 Hz), 9.51 (s, 1 H, H-10).

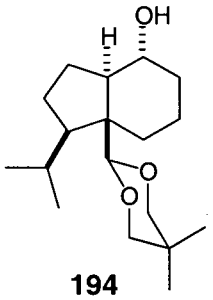
^{13}C NMR (100 MHz): δ = 19.0 (2 C, C-4' and C-5'), 20.9, 22.1, 22.5, 23.2, 28.1, 28.7, 31.7, 39.4, 47.2 (C-1), 52.0 (C-2'), 52.6, 55.9, 75.1 (C-10 or C-1'), 76.4 (C-10 or C-1'), 204.9 (C-3'), 213.8 (C-5).

Exact mass calculated for $C_{18}H_{31}O_3$ $[M+H]^+$: 295.2274; found 295.2278.

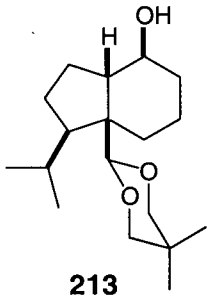
Optimized conditions for the hydroboration of alkene 195



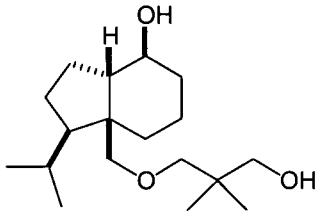
195



194



213



214

Small scale:

To a cold (0 °C), stirred solution of alkene **195** (65 mg, 0.23 mmol) in DCM (5 mL) was added, via a syringe, neat BH_3•SMe_2 (23 mg, 0.30 mmol). The reaction mixture was allowed to stir at this temperature for 6 h. After this time, H_2O (250 μL, 13.9 mmol) was added and the mixture was allowed to stir for 10 min. The reaction mixture was then treated with aq NaOH (3 M, 700 μL, 2.1 mmol) and aq H_2O_2 (8.8 M, 250 μL, 2.2 mmol). The mixture was allowed to stir overnight. Neat AcOH (120 μL, 2.1 mmol) was added. The phases were separated and the organic phase was washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (5 g of silica gel, 1:1 petroleum ether-Et_2O) to yield an inseparable mixture of alcohols **194** and **213** (36 mg, ratio 2:1, 52%, 96% based on recovered starting material) as a clear oil. Alkene **195** (30 mg, 46%) was also recovered as a clear oil.

Large scale:

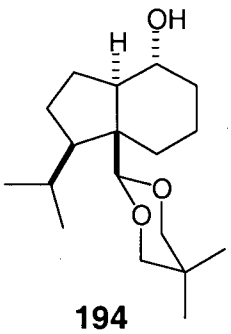
To a cold (0 °C), stirred solution of alkene **195** (2.16 g, 7.77 mmol) in DCM (167 mL) was added, via a syringe, neat BH_3•SMe_2 (1.18 mg, 15.5 mmol). The reaction mixture was allowed to stir at this temperature for 2 days. After this time, H_2O (7 mL, 390 mmol) was added and the reaction mixture was allowed to stir for 1 h. The mixture was then treated with aq NaOH (3 M, 20.7 mL, 62 mmol) and aq H_2O_2 (8.8 M, 7.1 mL, 62 mmol). The mixture was allowed to stir overnight. Neat AcOH (3.9 mL, 62 mmol) was added. The phases were separated and the organic phase was washed with brine (100 mL),

dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (100 g of silica gel, 1:1 petroleum ether-Et_2O) to yield an inseparable mixture of alcohols **194** and **213** (1.02 g, ratio 2:1, 44%, 69% based on recovered starting material) as a clear oil. Alkene **195** (777 mg, 2.80 mmol, 36%) was also recovered as a clear oil. In addition, elution of the column with Et_2O provided diol **214** (349 mg, 1.17 mmol, 15%) as a clear oil.

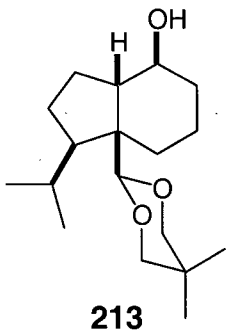
Oxidation of alcohols 194 and 213, preparation of

(1*S,6*R**,9*R**)-9-Isopropyl-5-oxobicyclo[4.3.0]nonane-1-carbaldehyde-2',2'-dimethylpropylene acetal (193) and**

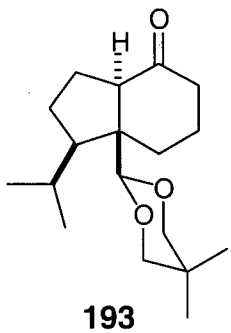
(1*S,6*S**,9*R**)-9-Isopropyl-5-oxobicyclo[4.3.0]nonane-1-carbaldehyde-2',2'-dimethylpropylene acetal (220)**



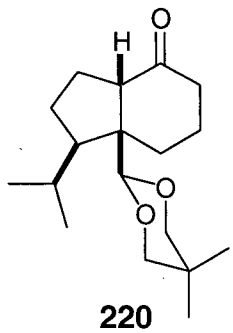
194



213



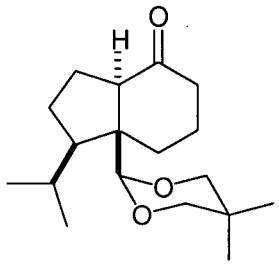
193



220

Alcohols **194** and **213** were oxidized to ketones **193** and **220**, respectively, using the method developed by Ley.[88] To a stirred solution of a mixture of alcohols **194** and **213** (ratio 1.5:1, 219 mg, 0.74 mmol) in DCM (15 mL) at r.t. was added, sequentially, NMO (130 mg, 1.11 mmol) in one portion and TPAP (26 mg, 0.07 mmol) in one portion. The reaction mixture was stirred overnight. The mixture was then filtered through a pad of silica gel (2 g) and the silica gel was rinsed with Et_2O. The collected eluate was concentrated. Purification of the residual oil by flash column chromatography (15 g of silica gel, 3:1 petroleum ether-Et_2O) provided ketone **193** (124 mg, 0.42 mmol, 57%) and ketone **220** (82 mg, 0.28 mmol, 38%) as clear oils.

(1*S,6*R**,9*R**)-9-Isopropyl-5-oxobicyclo[4.3.0]nonane-1-carbaldehyde-2',2'-dimethylpropylene acetal (193)**



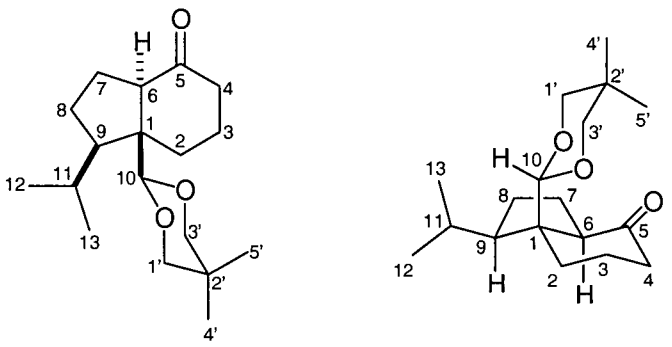
IR (film): ν = 2878, 1708, 1472, 1127, 1020, 914, 732 cm^{-1}.

^1H NMR (400 MHz): δ = 0.63 (s, 3 H), 0.81 (d, 3 H, J = 6.7 Hz), 0.97 (d, 3 H, J = 6.3 Hz), 1.11 (s, 3 H), 1.20-1.33 (m, 2 H), 1.33-1.50 (m, 2 H), 1.54-1.66 (m, 1 H), 1.66-1.76 (m, 1 H), 1.82-1.94 (m, 2 H), 2.01-2.11 (m, 1 H), 2.11-2.18 (dd, 1 H, J = 12.0, 7.3 Hz), 2.25-2.33 (dd, 1 H, J = 15.9, 5.9 Hz), 2.30-2.44 (m, 1 H), 2.60-2.69 (br d, 1 H, J = 14.5 Hz), 3.16-3.22 (d, 1 H, J = 11.0 Hz), 3.27-3.33 (d, 1 H, J = 11.0 Hz), 3.48-3.54 (dd, 1 H, J = 11.0, 2.7 Hz), 3.54-3.60 (dd, 1 H, J = 11.0, 2.7 Hz), 4.15 (s, 1 H).

^{13}C NMR (100 MHz): δ = 19.7 (+ve), 21.9, (−ve), 22.7 (−ve), 23.0 (−ve), 23.7 (−ve), 24.0 (+ve), 27.6 (+ve), 30.0 (+ve), 31.0 (−ve), 33.0 (+ve), 39.7 (+ve), 54.8 (+ve), 59.0 (−ve), 60.0 (−ve), 77.3 (+ve), 78.1 (+ve), 102.8 (−ve), 210.7 (+ve).

Exact mass calculated for $C_{18}H_{30}O_3$: 294.2195; found 294.2194.

Table 4.7: NMR data for (1*S**,6*R**,9*R**)-9-isopropyl-5-oxobicyclo[4.3.0]nonane-1-carbaldehyde-2',2'-dimethylpropylene acetal (**193**)



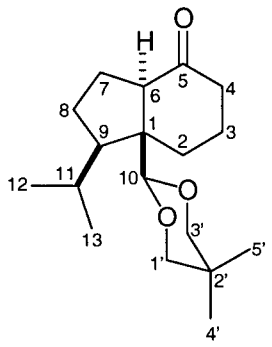
Carbon No.	^{13}C δ (ppm)[a]	^{1}H δ (ppm) (mult; *J* (Hz))[b,c,d]	HMBC Correlations[e]
1	54.8		H-2ax, H-2eq, H-3eq, H-6, H-7α, H-8α, H-12, H-13
2	33.0	H-2eq: 2.60-2.69 (m)	H-2ax, H-4ax, H-6
		H-2ax: part of the m at 1.20-1.33	
3	24.0	H-3eq: part of the m at 1.82-1.94	H-2eq, H-4ax, H-4eq
		H-3ax: 2.30-2.44 (m)	
4	39.7	H-4eq: 2.01-2.11 (m)	H-2ax, H-2eq, H-3ax, H-3eq, H-6
		H-4ax: 2.25-2.33 (dd, *J* = 15.9, 5.9)	
5	210.7		H-3eq, H-4ax, H-4eq, H-6, H-7β
6	60.0	H-6: 2.11-2.18 (dd, *J* = 12.0, 7.3)	H-2eq, H-4ax, H-7β
7	19.7	H-7β: 1.54-1.66 (dddd, *J* = 12.4, 12.4, 12.0, 6.4)	H-6
		H-7α: 1.66-1.76 (dddd, *J* = 13.1, 12.4, 7.3, 3.2)	
8	27.6	H-8β: part of the m at 1.33-1.50	H-7α, H-7β
		H-8α: part of the m at 1.82-1.94	
9	59.0	H-9: 1.20-1.33 (m)	H-6, H-8α, H-10, H-12, H-13
10	102.8	H-10: 4.15 (s)	H-2eq, H-6, H-9, H-1'ax, H-1'eq H-3'ax, H-3'eq
11	31.0	H-11: part of the m at 1.33-1.50	H-12, H-13
12	23.0	H-12: 0.97 (d, *J* = 6.3)	H-11, H-9
13	22.7	H-13: 0.81 (d, *J* = 6.7)	H-11, H-9
1'	77.3	H-1'ax: 3.27-3.33 (d, *J* = 11.0)	H-10, H-3'ax, H-3'eq, H-4', H-5'
		H-1'eq: 3.54-3.60 (dd, *J* = 11.0, 2.7)	
2'	30.0		H-1'eq, H-3'eq, H-4', H-5'
3'	78.1	H-3'ax: 3.16-3.22 (d, *J* = 11.0)	H-10, H-1'ax, H-1'eq, H-4', H-5'
		H-3'eq: 3.48-3.54 (d, *J* = 11.0, 2.7)	
4'	21.9	H-4': 0.63 (s)	H-1'ax, H-3'ax, H-5'
5'	23.7	H-5': 1.11 (s)	H-1'ax, H-1'eq, H-3'ax, H-3'eq, H-4'

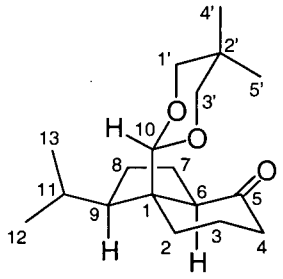
[a] Recorded at 100 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC and JMOD data.

[d] Methylene protons are designated H-Xax and H-Xeq if they are known to occupy axial and equatorial positions, respectively, in the conformation depicted above. Methylene protons are designated H-Xα if they are known to reside below the plane of the paper in the structure depicted above. They are designated H-Xβ if they are known to reside above the plane of the paper in the structure depicted above.

[e] Only those correlations which could be unambiguously assigned are recorded.

Table 4.8: NMR data for (1*S**,6*R**,9*R**)-9-isopropyl-5-oxobicyclo[4.3.0]nonane-1-carbaldehyde-2',2'-dimethylpropylene acetal (**193**)





Proton No	^{1}H δ (ppm) (mult; *J* (Hz))[a,b,c]	COSY Correlations[d]	NOE Correlations[e]
H-2eq	2.60-2.69 (m)	H-2ax, H-3ax, H-3eq	H-3ax, H-3eq, H-2ax, H-12
H-2ax	part of the m at 1.20-1.33	H-2eq, H-3ax, H-3eq	
H-3eq	part of the m at 1.82-1.94	H-2ax, H-2eq, H-3ax, H-4ax, H-4eq	
H-3ax	2.30-2.44 (m)	H-2ax, H-2eq, H-3eq, H-4ax, H-4eq	
H-4eq	2.01-2.11 (m)	H-4ax, H-3ax, H-3eq	
H-4ax	2.25-2.33 (dd, *J* = 15.9, 5.9)	H-4eq, H-3ax, H-3eq	
H-6	2.11-2.18 (dd, *J* = 12.0, 7.3)	H-7α, H-7β	
H-7β	1.54-1.66 (dddd, *J* = 12.4, 12.4, 12.0, 6.4)	H-6, H-7α, H-8α, H8β	
H-7α	1.66-1.76 (dddd, *J* = 13.1, 12.4, 7.3, 3.2)	H-6, H-7β, H-8α, H-8β	
H-8β	part of the m at 1.33-1.50	H-7α, H-7β	
H-8α	part of the m at 1.82-1.94	H-7α, H-7β	
H-9	1.20-1.33 (m)		
H-10	4.15 (s)		H-7β, H-8β, H-11, H-1'ax, H-3'ax
H-11	part of the m at 1.33-1.50	H-12, H-13	
H-12	0.97 (d, *J* = 6.3)	H-11	
H-13	0.81 (d, *J* = 6.7)	H-11	
H-1'ax	3.27-3.33 (d, *J* = 11.0)	H-1'eq	
H-1'eq	3.54-3.60 (dd, *J* = 11.0, 2.7)	H-1'ax	
H-3'ax	3.16-3.22 (d, *J* = 11.0)	H-3'eq	
H-3'eq	3.48-3.54 (d, *J* = 11.0, 2.7)	H-3'ax	
H-4'	0.63 (s)		
H-5'	1.11 (s)		

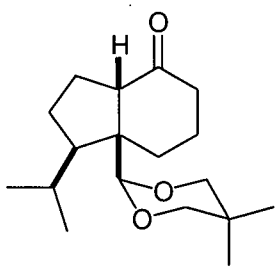
[a] Recorded at 400 MHz. [b] Assignments based on HMQC and JMOD data.

[c] Methylene protons are designated H-Xax and H-Xeq if they are known to occupy axial and equatorial positions, respectively, in the conformation depicted above. Methylene protons are designated H-Xα if they are known to reside below the plane of the paper in the structure depicted above. They are designated H-Xβ if they are known to reside above the plane of the paper in the structure depicted above.

[d] Only those correlations which could be unambiguously assigned are recorded.

[e] Recorded as NOE difference at 400 MHz using 1D selective NOE experiments.

(1*S,6*S**,9*R**)-9-Isopropyl-5-oxobicyclo[4.3.0]nonane-1-carbaldehyde-2',2'-dimethylpropylene acetal (220)**



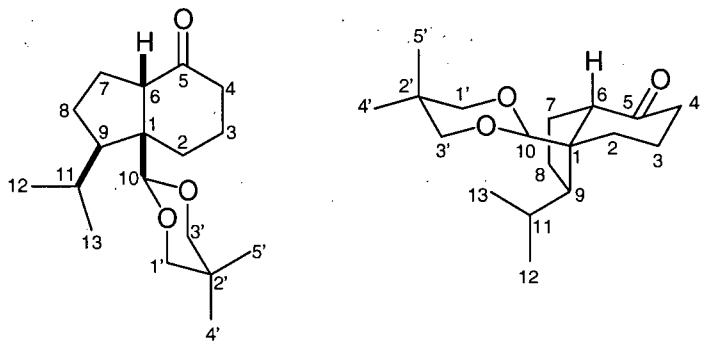
IR (film): ν = 2937, 1708, 1471, 1121, 994, 734 cm^{-1}.

^1H NMR (400 MHz): δ = 0.59 (s, 3 H), 0.78 (d, 3 H, J = 6.7 Hz), 0.89 (d, 3 H, J = 6.7 Hz), 1.11 (s, 3 H), 1.33-1.45 (m, 2 H), 1.58-1.71 (m, 2 H), 1.66-1.81 (m, 3 H), 1.81-1.92 (m, 1 H), 1.92-2.07 (m, 2 H), 2.14-2.24 (m, 1 H), 2.25-2.34 (m, 1 H), 2.86-2.92 (dd, 1 H, J = 7.5, 7.5 Hz), 3.25-3.32 (d, 1 H, J = 11.1 Hz), 3.29-3.35 (d, 1 H, J = 11.1), 3.49-3.58 (br d, 2 H, J = 11.1 Hz), 4.27 (s, 1 H).

^{13}C NMR (100 MHz): δ = 21.0 (+ve), 21.7 (−ve), 22.1 (−ve), 23.1 (−ve), 23.6 (−ve), 24.7 (+ve), 27.9 (+ve), 28.4 (−ve), 29.1 (+ve), 30.0 (+ve), 38.9 (+ve), 54.0 (−ve), 54.4 (+ve), 54.5 (−ve), 77.0 (+ve), 77.2 (+ve), 104.3 (−ve), 214.4 (+ve).

Exact mass calculated for $C_{18}H_{30}O_3$: 294.2195; found 294.2200.

Table 4.9: NMR data for (1*S**,6*S**,9*R**)-9-isopropyl-5-oxobicyclo[4.3.0]nonane-1-carbaldehyde-2',2'-dimethylpropylene acetal (**220**)



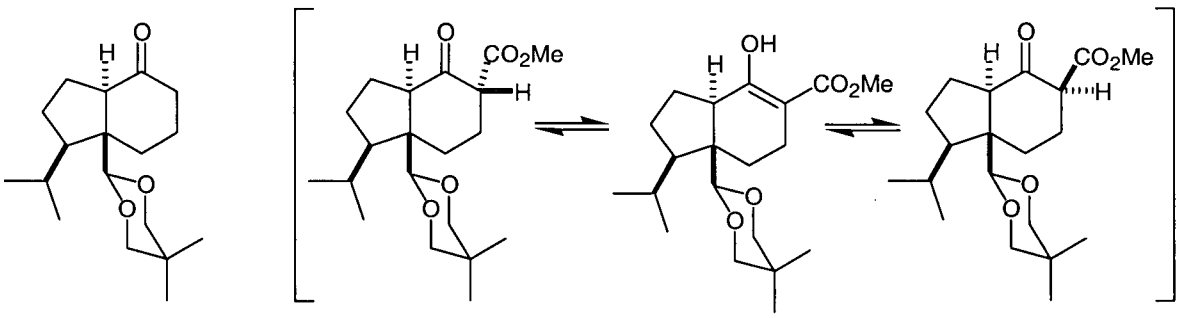
Carbon No.	^{13}C δ (ppm)[a]	^{1}H δ (ppm) (mult; *J* (Hz))[b,c,d]	HMBC Correlations
1	54.4		H-2a, H-2b, H-9, H-10
2	29.1	H-2a: part of the m at 1.58-1.71	H-10, H-4ax, H-4eq
		H-2b: part of the m at 1.92-2.07	
3	21.0	H-3a: part of the m at 1.66-1.81	H-2a, H-2b, H-4ax, H-4eq
		H-3b: part of the m at 1.92-2.07	
4	38.9	H-4ax: 2.14-2.24 (ddd, *J* = 14.7, 8.3, 6.1)	H-3a, H-3b
		H-4eq: 2.25-2.34 (ddd, *J* = 14.7, 5.9, 5.9)	
5	214.4		H-3b, H-4ax, H-4eq, H-6, H-7b
6	54.5	H-6: 2.86-2.93 (dd, *J* = 7.5, 7.5)	H-3a, H-3b, H-4eq
7	24.7	H-7a: part of the m at 1.58-1.71	H-6, H-8a, H-8b
		H-7b: part of the m at 1.81-1.92	
8	27.9	H-8a: part of the m at 1.33-1.45	H-6, H-9
		H-8b: part of the m at 1.66-1.81	
9	54.0	H-9: part of the m at 1.33-1.45	H-8a, H-8b, H-11, H-12, H-13
10	104.3	H-10: 4.27 (s)	H-2a, H-2b, H-6, H-9, H-1'ax, H-1'eq, H-3'ax, H-3'eq
11	28.4	H-11: part of the m at 1.66-1.81	H-12, H-13
12	22.1	H-12: 0.78 (d, *J* = 6.7)	H-9, H-11
13	23.6	H-13: 0.89 (d, *J* = 6.7)	H-9, H-11
1'	77.0	H-1'ax: 3.29-3.35 (d, *J* = 11.1)	H-10, H-3'ax, H-3'eq, H-4', H-5'
		H-1'eq: part of the br. d at 3.49-3.58	
2'	30.0		H-1'eq, H-3'eq, H-4', H-5'
3'	77.2	H-3'ax: 3.25-3.32 (d, *J* = 11.1)	H-10, H-1'ax, H-1'eq, H-4', H-5'
		H-3'eq: part of the br. d at 3.49-3.58	
4'	21.7	H-4': 0.59 (s)	H-1'ax, H-3'ax, H-5'
5'	23.1	H-5': 1.11 (s)	H-1'ax, H-1'eq, H-3'ax, H-3'eq, H-4'

[a] Recorded at 100 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC and JMOD data.

[d] Methylene protons are designated H-Xax and H-Xeq if they are known to occupy axial and equatorial positions, respectively, in the conformation depicted above. If no information regarding their position is available then they are arbitrarily designated H-Xa and H-Xb.

Methyl (1*R,3*S**,6*S**,7*R**)-6-formyl-7-isopropyl-2-oxobicyclo-[4.3.0]nonane-3-carboxylate 2',2'-dimethylpropylene acetal (189) and**

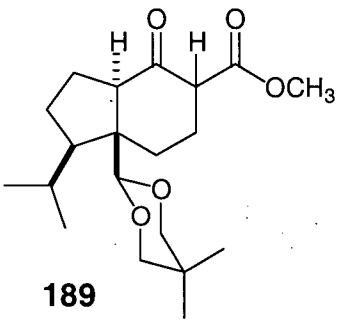
Methyl (1*R,3*R**,6*S**,7*R**)-6-formyl-7-isopropyl-2-oxobicyclo-[4.3.0]nonane-3-carboxylate 2',2'-dimethylpropylene acetal (189)**



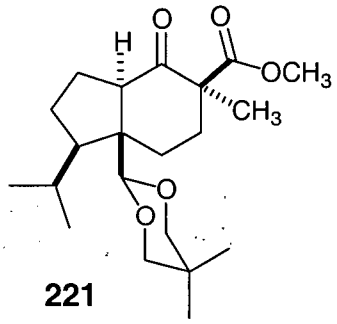
193 **189**

To a cold (–78 °C) solution of LDA (0.823 mmol) in THF (5 mL) was added a cold (–78 °C) solution of ketone **193** (121 mg, 0.411 mmol) in THF (2 mL). The resulting solution is allowed to stir at this temperature for 1.5 h. Neat methyl cyanoformate (Manders reagent,[113] 38 mg, 0.45 mmol) was added drop-wise, via a syringe, and the solution was allowed to warm to r.t. TLC analysis of the mixture revealed that ketone **193** had been consumed and that two new materials had been formed. Sat. aq NH_4Cl (10 mL) and Et_2O (10 mL) were added and the phases were allowed to separate. The organic phase was washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The ^1H NMR spectrum of the acquired material revealed the presence of more than two products. Attempts to separate the two materials by flash column chromatography on silica gel failed. Attempts to characterize the mixture of products by GC-LRMS were not successful.

Methyl (1*R,3*S**,6*S**,7*R**)-6-formyl-7-isopropyl-3-methyl-2-oxobicyclo-[4.3.0]nonane-3-carboxylate 2',2'-dimethylpropylene acetal (221)**



189



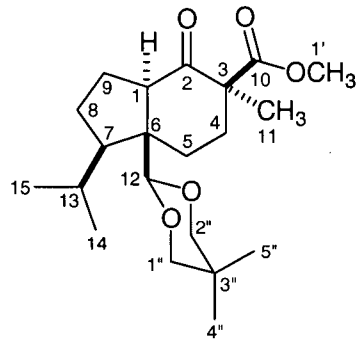
221

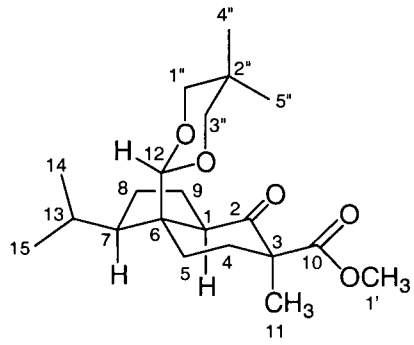
To a stirred solution of keto ester **189** (70 mg, 0.20 mmol) in THF (5 mL) at r.t was added NaH (16 mg of a 60% dispersion in mineral oil, 0.40 mmol). The resulting reaction mixture was stirred for 10 min. Neat MeI (280 mg, 3.29 mmol) was added drop-wise, via a syringe, and the reaction mixture was allowed to stir overnight. H_2O (5 mL) and Et_2O (5 mL) were added and the layers were separated. The organic layer was washed with brine (5 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (4 g of silica gel, 3:2 petroleum ether-Et_2O) to provide keto ester **221** (51 mg, 0.14 mmol, 70%) as a clear oil.

^{1}H NMR (400 MHz): δ = 0.67 (s, 3 H), 0.83 (d, 3 H, J = 6.6 Hz), 0.99 (d, 3 H, J = 6.3 Hz), 1.20 (s, 3 H), 1.28-1.36 (ddd, 1 H, J = 9.4, 9.4, 9.4 Hz), 1.36-1.52 (m, 2 H),1.40 (s, 3 H), 1.53-1.64 (m, 2 H), 1.64-1.74 (m, 2 H), 1.86-1.97 (dddd, 1 H, J = 13.2, 9.5, 9.4, 6.7 Hz), 2.38-2.43 (dd, 1 H, J = 11.8, 7.2 Hz), 2.62-2.68 (ddd, 1 H, J = 13.6, 5.0, 2.5 Hz), 3.09-3.18 (ddd, 1 H, J = 13.8, 13.8, 5.0 Hz), 3.20-3.25 (d, 1 H, J = 11.1 Hz), 3.32-3.36 (d, 1 H, J = 11.1 Hz), 3.51-3.56 (dd, 1 H, J = 11.1, 2.8 Hz), 3.58-3.62 (dd, 1 H, J = 11.1, 2.8 Hz), 3.69 (s, 3 H), 4.20 (s, 1 H).

^{13}C NMR (100 MHz): δ = 19.9, 22.1, 22.7, 23.0, 23.4, 23.7, 27.7, 29.4, 30.0, 30.0, 31.0, 34.5, 51.9, 55.5, 57.0, 58.0, 77.3, 77.9, 101.8, 174.3, 208.5.

Table 4.10: NMR data for methyl (1*R**,3*S**,6*S**,7*R**)-6-formyl-7-isopropyl-3-methyl-2-oxobicyclo[4.3.0]nonane-3-carboxylate 2',2'-dimethylpropylene acetal (**221**)

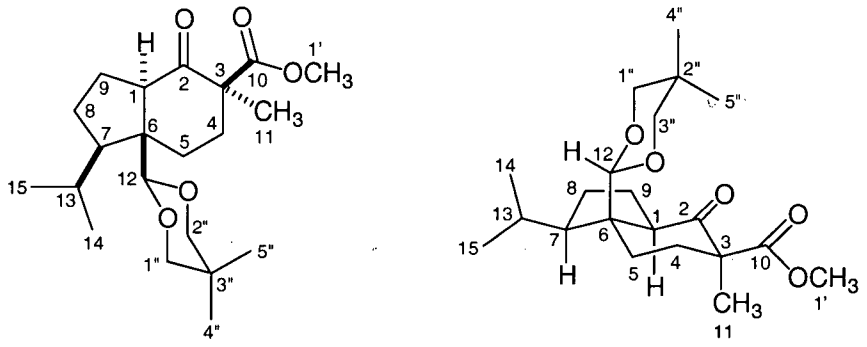




Carbon No.	^{13}C δ (ppm)[a]	^{1}H δ (ppm) (mult; *J* (Hz))[b,c,d]	HMBC Correlations
1	55.5	H-1: 2.38-2.43 (dd, *J* = 11.8, 7.2)	H-5b, H-9a
2	208.5		H-1, H-11
3	57.0		H-4b, H-11
4	34.5	H-4a: part of the m at 1.64-1.74 (ddd, *J* = 13.8, 4.6, 2.5)	H-11
		H-4b: 3.09-3.18 (ddd, *J* = 13.8, 13.8, 5.0)	
5	30.0	H-5a: part of the m at 1.36-1.52 (ddd, *J* = 13.8, 13.6, 4.6)	H-1, H-4b, H-12
		H-5b: 2.62-2.68 (ddd, *J* = 13.6, 5.0, 2.5)	
6	29.4		
7	58.8	H-7: 1.28-1.36 (ddd, *J* = 9.4, 9.4, 9.4)	H-12, H-14, H-15
8	27.7	H-8a: part of the m at 1.53-1.64	H-7
		H-8b: 1.86-1.97 (dddd, *J* = 13.2, 9.5, 9.4, 6.7)	
9	19.9	H-9a: part of the m at 1.53-1.64	H-1, H-8a
		H-9b: part of the m at 1.64-1.74	
10	174.3		H-4b, H-1',
11	243	H-11: 1.40 (s)	H-4a, H-4b
12	101.8	H-12: 4.20 (s)	H-1, H-5a, H-1"a, H-1"b, H-3"b
13	31.0	H-13: part of the m at 1.36-1.52	H-14, H-15
14	22.7	H-14: 0.99 (d, *J* = 6.3)	H-15
15	23.0	H-15: 0.83 (d, *J* = 6.6)	H-14
1'	51.9	H-1': 3.69 (s)	
1"	77.3	H-1"a: 3.32-3.36 (d, 11.0)	H-12, H-3"a, H-3"b, H4", H-5"
		H-1"b: 3.58-3.62 (dd, *J* = 11.0, 2.8)	
2"	30.0		H-4", H-5"
3"	77.9	H-3"a: 3.20-3.25 (d, *J* = 11.1)	H-12, H-1"a, H-1"b, H-4", H-5"
		H-3"b: 3.51-3.56 (d, *J* = 11.1, 2.8)	
4"	22.1	0.67 (s)	H-1"a, H-3"a, H-5"
5"	23.7	1.20 (s)	H-1"a, H-3"a, H-4"

[a] Recorded at 100 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC data.
[d] Methylene protons are designated H-Xa and H-Xb arbitrarily.

Table 4.11: NMR data for methyl (1*R**,3*S**,6*S**,7*R**)-6-formyl-7-isopropyl-3-methyl-2-oxobicyclo[4.3.0]nonane-3-carboxylate 2',2'-dimethylpropylene acetal (**221**)



Proton No	^{1}H δ (ppm) (mult; *J* (Hz))[a,b,c]	COSY Correlations[d]	NOE Correlations[e]
H-1	2.38-2.43 (dd, *J* = 11.8, 7.2)	H-9a, H-9b	H-7, H-11, H-5a
H-4a	part of the m at 1.64-1.74 (ddd, *J* = 13.8, 4.6, 2.5)	H-4b, H-5a, H-5b	
H-4b	3.09-3.18 (ddd, *J* = 13.8, 13.8, 5.0)	H-4a, H-5a, H-5b	H-4a, H-5", H-5b
H-5a	part of the m at 1.36-1.52 (ddd, *J* = 13.8, 13.6, 4.6)	H-4a, H-4b, H-5b	
H-5b	2.62-2.68 (ddd, *J* = 13.6, 5.0, 2.5)	H-4a, H-4b, H-5a	H-4a, H-4b, H-5a, H-14
H-7	1.28-1.36 (ddd, *J* = 9.4, 9.4, 9.4)	H-8b	
H-8a	part of the m at 1.53-1.64	H-8b	
H-8b	1.86-1.97 (dddd, *J* = 13.2, 9.5, 9.4, 6.7)	H-7, H-8a	
H-9a	part of the m at 1.53-1.64	H-1	
H-9b	part of the m at 1.64-1.74	H-1	
H-11	1.40 (s)		
H-12	4.20 (s)		
H-13	part of the m at 1.36-1.52	H-14, H-15	
H-14	0.99 (d, *J* = 6.3)	H-13	
H-15	0.83 (d, *J* = 6.6)	H-13	
H-1'	3.69 (s)		
H-1"a	3.32-3.36 (d, 11.0)	H-1"b	
H-1"b	3.58-3.62 (dd, *J* = 11.0, 2.8)	H-1"a, H-3"b	
H-3"a	3.20-3.25 (d, *J* = 11.1)	H-3"b	
H-3"b	3.51-3.56 (d, *J* = 11.1, 2.8)	H-1"b, H-3"a	
H-4"	0.67 (s)		
H-5"	1.20 (s)		

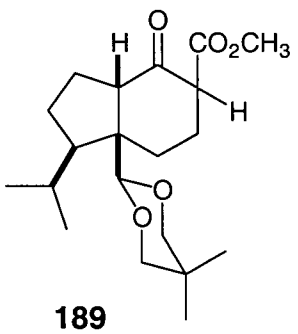
[a] Recorded at 400 MHz. [b] Assignments based on HMQC data.

[c] Methylene protons are designated H-Xa and H-Xb arbitrarily.

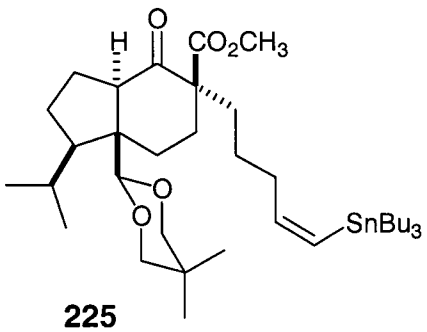
[d] Only those correlations which could be unambiguously assigned are recorded.

[e] Recorded as NOE difference at 400 MHz using 1D selective NOE experiments.

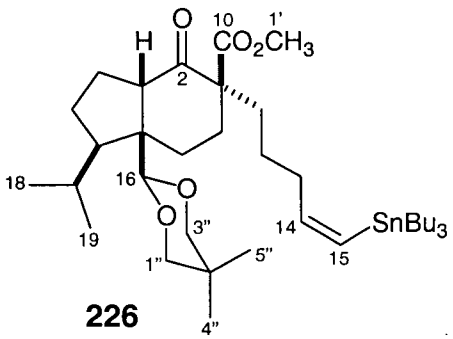
Methyl (1*R,3*S**,6*S**,7*R**)-6-formyl-7-isopropyl-3-[(*Z*)-5-tri-*n*-butylstannylpent-4-enyl]-2-oxobicyclo[4.3.0]nonane-3-carboxylate 2',2'-dimethylpropylene acetal (226)**



189



225



226

To a stirred solution of keto ester **189** (116 mg, 0.33 mmol) in THF (5 mL) at r.t. was added, via a syringe, KHMDS (0.66 mL of a 0.5 M solution in toluene, 0.33 mmol). The resulting mixture was stirred for 30 min. A solution of *cis*-5-iodo-1-tributylstannylpent-1-ene (160 mg, 0.33 mmol) in THF (1 mL) was transferred to the reaction vessel via a cannula. The resulting reaction mixture was heated to reflux overnight. Sat. aq $NaHCO_3$ (5 mL) and Et_2O (5 mL) were added and the layers were separated. The organic layer was washed with brine (5 mL), dried ($MgSO_4$) and concentrated. The acquired oil was purified by flash column chromatography (10 g of silica gel, 9:1 petroleum ether-Et_2O) to provide an inseparable mixture of keto esters **225** and **226** (ratio 4:5, 161 mg, 0.23 mmol, 69%) as a clear oil.

To a stirred solution of keto esters **225** and **226** (161 mg, 0.23 mmol) in MeOH (2 mL) was added NaOMe (95%, 20 mg, 0.37 mmol). The resulting reaction mixture was heated to reflux for 18 h. Sat. aq NH_4Cl (5 mL) and Et_2O (5 mL) were added and the layers were separated. The organic layer was washed with brine (5 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (10 g of silica gel, 9:1 petroleum ether-Et_2O) to provide keto ester **226** (145 mg, 0.20 mmol, 90%) as a clear oil.

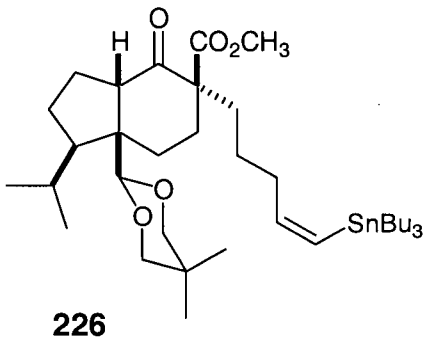
IR (film): ν = 2954, 1736, 1709, 1459, 1111 cm^{-1}.

^1H NMR (400 MHz): δ = 0.66 (s, 3 H, Me-4" or Me-5"), 0.77 (d, 3 H, J = 6.6 Hz, Me-18 or me-19), 0.79-0.89 (m, 12 H), 0.91 (d, 3 H, J = 6.6 Hz, Me-18 or Me-19), 1.13 (s, 3 H, Me-4" or Me-5"), 1.15-1.17 (m, 23 H), 1.71-1.85 (m, 2 H), 1.85-1.94 (ddd, 1 H, J = 13.2, 13.2, 4.5 Hz), 1.94-2.05 (m, 2 H), 2.05-2.20 (m, 2 H), 2.41-2.51 (ddd, 1 H, J = 14.0, 5.3, 4.0 Hz), 3.10-3.15 (dd, 1 H, J = 7.7, 2.3 Hz), 3.30 (d, 1 H, J = 10.0 Hz, H-1"ax or H-3" ax), 3.33 (d, 1 H, J = 10.0 Hz, H-1"ax or H-3"ax), 3.52-3.57 (dd, 1 H, J = 10.0, 2.9 Hz, H-1"eq or H-3"eq), 3.54-3.59 (dd, 1 H, J = 10.0, 2.9 Hz, H-1"eq or H-3"eq), 3.66 (s, 3 H, Me-1'), 4.18 (s, 1 H, H-16), 5.76 (d, 1 H, J = 12.5 Hz; $^2J_{Sn\text{-}H}$ = 36 Hz, H-15), 6.41-6.50 (ddd, 1 H, J = 13.9, 12.5, 7.0 Hz; $^3J_{Sn\text{-}H}$ = 71 Hz, H-14).

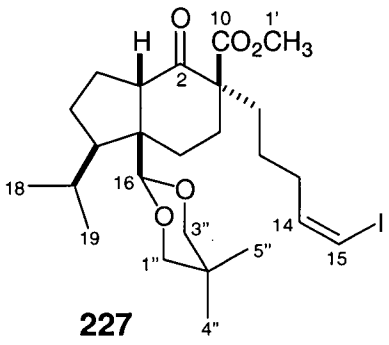
^{13}C NMR (100 MHz): δ = 10.2 (+ve, 3 C), 13.7 (−ve, 3 C), 21.0 (+ve), 21.7 (−ve), 22.8 (−ve), 23.2 (−ve), 23.3 (−ve), 24.2 (+ve), 24.8 (+ve), 27.3 (+ve, 3 C), 27.9 (+ve), 29.2 (+ve, 3 C), 29.3 (−ve), 30.0 (+ve), 30.2 (+ve), 34.8 (+ve), 37.3 (+ve), 50.9 (−ve), 52.1 (−ve), 53.9 (−ve), 56.2 (+ve), 59.3 (+ve), 77.2 (+ve, C-1"), 77.3 (+ve, C-3"), 103.1 (−ve, C-16), 128.4 (−ve), 148.5 (−ve), 172.4 (+ve, C-10), 209 (+ve, C-2).

Exact mass calculated for $C_{33}H_{57}O_5{}^{120}Sn$ $[M-Bu]^+$: 653.3228; found: 653.3226.
$C_{33}H_{57}O_5{}^{118}Sn$ $[M-Bu]^+$: 651.3222; found: 651.3215.
$C_{33}H_{57}O_5{}^{116}Sn$ $[M-Bu]^+$: 649.3223; found: 649.3226.

Methyl (1*R,3*S**,6*S**,7*R**)-6-formyl-3-[(*Z*)-5-iodopent-4-enyl]-7-isopropyl-2-oxobicyclo[4.3.0]nonane-3-carboxylate 2',2'-dimethylpropylene acetal (227)**



226



227

To a stirred solution of alkenylstannane **226** (318 mg, 0.45 mmol) in dry DCM (10 mL) at r.t. was added a solution of iodine (136 mg, 0.54 mmol) in dry DCM (10 mL). The reaction mixture was stirred at r.t. for 15 min. Sat. aq $Na_2S_2O_3$ (20 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (10 mL). The organic layers were combined and washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (15 g of silica gel, 19:1 petroleum ether-Et_2O) to provide alkenyl iodide **227** (220 mg, 90%) as a clear oil.

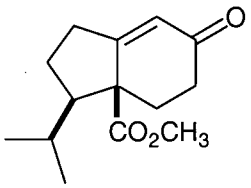
IR (film): ν = 2954, 1736, 1709, 1459, 1111 cm^{-1}.

^1H NMR (400 MHz): δ = 0.68 (s, 3 H, Me-4" or Me-5"), 0.80 (d, 3 H, J = 6.6 Hz, Me-18 or Me-19), 0.92 (d, 3 H, J = 6.6 Hz, Me-18 or Me-19), 1.14 (s, 3 H, Me-4" or Me-5"), 1.24-1.48 (m, 4 H), 1.62-1.99 (m, 7 H), 2.00-2.21 (m, 5 H), 3.07-3.13 (dd, 1 H, J = 8.6, 6.5 Hz), 3.32 (d, 1 H, J = 10.8 Hz, H-1"ax or H-3"ax), 3.35 (d, 1 H, J = 10.8 Hz, H-1"ax or H-3"eq), 3.52-3.59 (dd, 1 H, J = 10.8, 2.8 Hz, H-1"eq or H-3"eq), 3.55-3.62 (dd, 1 H, J = 10.8, 2.8 Hz, H-1"eq or H-3"eq), 3.67 (s, 3 H, Me-1'), 4.30 (s, 1 H, H-16), 6.10-6.20 (m, 2 H, H-14 and H-15).

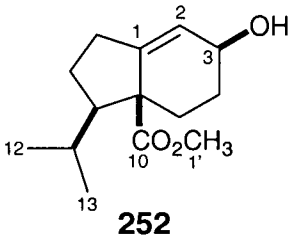
^{13}C NMR (100 MHz): δ = 21.7 (−ve), 22.2 (−ve), 22.9 (+ve), 23.3 (−ve), 23.7 (−ve), 24.6 (+ve), 26.7 (+ve), 28.2 (+ve), 28.5 (−ve), 28.9 (+ve), 30.0 (+ve), 33.7 (+ve), 34.8 (+ve), 52.1 (−ve), 52.5 (−ve), 54.3 (+ve), 55.6 (−ve), 59.1 (+ve), 77.1 (+ve, C-1" or C-3"), 77.2 (+ve, C-1" or C-3"), 82.8 (−ve, C-15), 104.5 (−ve, C-16), 140.7 (−ve, C-14), 173.1 (+ve, C-10), 211.0 (+ve, C-2).

Exact mass calculated for $C_{25}H_{39}IO_5$: 546.1842; found: 546.1842.

Methyl (3*S,6*S**,7*R**)-3-hydroxy-7-isopropylbicyclo[4.3.0]non-1-ene-6-carboxylate (252)**



197



252

To a stirred solution of enone **197** (543 mg, 2.3 mmol) and $CeCl_3 \bullet 7H_2O$ (1.028 g, 2.8 mmol) in MeOH (65 mL) at r.t. was added $NaBH_4$ (104 mg, 2.7 mmol) in four portions over 10 min. TLC analysis of the reaction mixture indicated that all of the starting material had been consumed shortly after all of the reducing agent had been added. Aq HCl (10% HCl, 5.5 mL) was added and the reaction mixture was stirred for 10 min. H_2O (50 mL) and Et_2O (50 mL) were added and the phases were separated. The organic phase was washed with sat. aq $NaHCO_3$ (25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (25 g of silica gel, 3:2 Et_2O-petroleum ether) to yield alcohol **252** (471 mg, 2.0 mmol, 86%) as a clear oil.

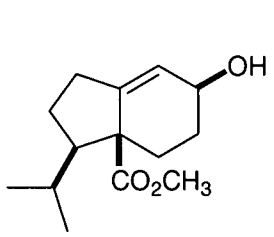
IR (film): ν = 3382, 2954, 1726, 1434, 1166, 1006 cm^{-1}.

^1H NMR (300 MHz): δ = 0.83 (d, 3 H, J = 6.2 Hz, Me-12 or Me-13), 0.99 (d, 3 H, J = 6.1 Hz, Me-12 or Me-13), 1.51-1.61 (m, 6 H), 1.81-1.94 (m, 1 H), 2.04-2.13 (m, 1 H), 2.16-2.32 (m, 1 H), 2.59-2.74 (m, 2 H), 3.66 (s, 3 H, Me-1'), 4.22 (br. s, 1 H, H-3), 5.46 (s, 1 H, H-2).

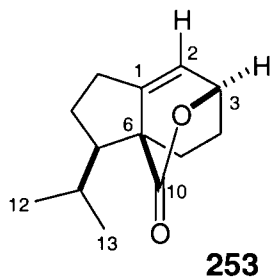
^{13}C NMR (100 MHz): δ = 22.3 (C-12 or C-13), 22.4 (C-12 or C-13), 27.4, 29.3, 31.3 (2 C), 33.6, 51.6, 56.0, 58.7 (C-1'), 68.1, 123.9 (C-2), 148.2 (C-1), 174.1 (C-10)

Exact mass calculated for $C_{14}H_{22}O_3$: 238.1569; found: 238.1573.

(3S*,6S*,7R*)-7-Isopropylbicyclo[4.3.0]non-1-ene-6,3-carbolactone (253)



252



253

To a stirred solution of alcohol **252** (84 mg, 0.35 mmol) in THF (5 mL) at r.t. was added dry KH (16 mg, 0.4 mmol) in one portion. After 30 min, TLC analysis of the mixture indicated that all the starting material had been consumed. H_2O (5 mL) and Et_2O (5 mL) were added and the phases were separated. The organic phase was washed with brine (5 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (5 g of silica gel, 1:1 petroleum ether-Et_2O) to yield lactone **253** (66 mg, 0.32 mmol, 91%) as a clear oil.

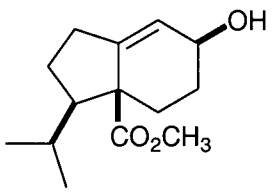
IR (film): ν = 2958, 1742, 1473, 1363, 1064 cm^{-1}.

^1H NMR (300 MHz): δ = 0.95 (d, 3 H, J = 6.7 Hz, Me-12 or Me-13), 1.00 (d, 3 H, J = 6.5 Hz, Me-12 or Me-13), 1.20-1.28 (dd, 1 H, J = 11.2, 7.2 Hz), 1.40-1.61 (m, 2 H), 1.65-1.75 (m, 1 H), 2.05-2.31 (m, 4 H), 2.34-2.45 (dd, 1 H, J = 16.6, 6.9 Hz), 2.63-2.82 (m, 1 H), 5.03-3.11 (ddd, 1 H, J = 5.0, 3.7, 1.1 Hz, H-3), 6.06-6.12 (ddd, 1 H, J = 5.0, 2.7, 1.5 Hz, H-2).

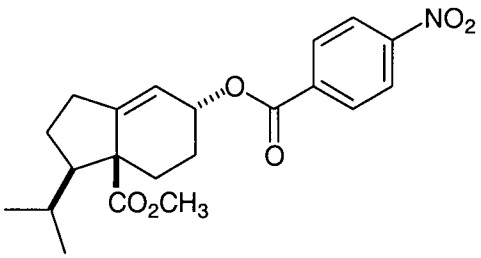
^{13}C NMR (100 MHz): δ = 23.1 (−ve, C-12 or C-13), 23.5 (−ve, C-12 or C-13), 27.6 (+ve), 28.1 (+ve), 28.1 (+ve), 28.4 (−ve), 32.7 (+ve), 54.6 (+ve, C-6), 55.4, (−ve), 74.3 (−ve, C-3), 120.8 (−ve, C-2), 154.1 (+ve, C-1), 174.2 (C-10).

Exact mass calculated for $C_{13}H_{18}O_2$: 206.1307; found: 2061310.

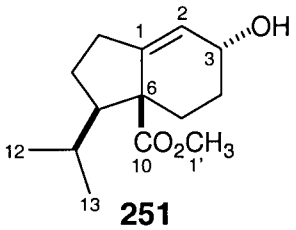
Methyl (3*R,6*S**,7*R**)-3-hydroxy-7-isopropylbicyclo[4.3.0]non-1-ene-6-carboxylate (251)**



252



254



251

Alcohol **252** was converted to alcohol **251** using the method developed by Mitsunobu.[128] Thus, to a cold (0 °C), stirred, solution of alcohol **252** (617 mg, 2.59 mmol), *p*-nitrobenzoic acid (866 mg, 5.18 mmol), and Ph_3P (1.36 g, 5.18 mmol) in THF (55 mL) was added, drop-wise, via a syringe, neat DEAD (990 mg, 5.68 mmol). The reaction mixture was allowed to warm up to r.t. overnight. The reaction mixture was concentrated and the residual material was purified by flash column chromatography (50 g of silica gel, 3:1 petroleum ether-Et_2O) to provide ester (**254**). This material was dissolved in methanol (20 mL) and the resulting solution was treated with NaOMe (95%, 270 mg, 4.7 mmol). After 1 h, H_2O (30 mL) and Et_2O (30 mL) were added. The phases were separated and the organic phase was washed with brine (30 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (35 g of silica gel, 3:2 Et_2O-petroleum ether) to yield alcohol **251** (553 mg, 2.32 mmol, 89%) as a clear oil.

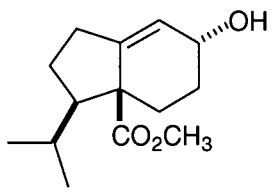
IR (film): ν = 3428, 2953, 1725, 1436, 1169, 1011 cm^{-1}.

^1H NMR (400 MHz): δ = 0.83 (d, 3 H, J = 5.9 Hz, Me-12 or Me-13), 1.01 (d, 3 H, J = 5.8 Hz, Me-12 or Me-13), 1.26-1.36 (ddd, 1 H, J = 13.3, 13.3, 3.1 Hz), 1.36-1.57 (m, 3 H), 1.59-1.81 (m, 3 H), 1.82-1.91 (m, 1 H), 2.21-2.32 (m, 1 H), 2.49-2.57 (ddd, 1 H, J = 16.3, 3.1, 3.1 Hz), 2.58-2.69 (m, 1 H), 3.60 (s, 3 H, Me-1'), 4.06 (br. s, 1 H, H-3), 5.53 (d, 1 H, J = 1.5 Hz, H-2).

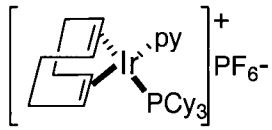
^{13}C NMR (100 MHz): δ = 22.2 (−ve, C-12 or C-13), 22.5 (−ve, C-12 or C-13), 27.2 (+ve), 28.2 (+ve), 29.6 (2 C, +ve), 31.1 (−ve), 51.4 (−ve), 55.9 (+ve, C-6), 58.7 (−ve), 63.3 (−ve), 121.8 (−ve, C-2), 148.6 (+ve, C-1), 173.7 (+ve, C-10).

Exact mass calculated for $C_{14}H_{22}O_3$: 238.1569; found 238.1570.

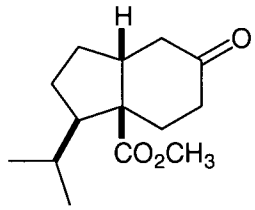
Methyl (1*R,6*R**,9*R**)-9-isopropyl-4-oxobicyclo[4.3.0]nonane-1-carboxylate (256)**



251



Crabtree's catalyst



256

A stirred solution of alcohol **251** (469 mg, 1.97 mmol) and Crabtree's catalyst (10 mg, 0.12 mmol) in DCM (10 mL) at r.t. and the atmosphere in the reaction vessel was purged with H_2 (g). During the purge, the solution turned from orange to pale yellow in colour. The mixture was allowed to stir for 24 h under H_2 (g) at 1 atmosphere. TLC analysis of the mixture indicated that all the starting material had been consumed. The mixture was filtered through a pad of silica gel (10 g) and the silica gel was rinsed with Et_2O. The collected eluate was concentrated and the residual oil was purified by flash column chromatography (25 g of silica gel, 1:1 petroleum ether-Et_2O) to provide ketone **256** (366 mg, 1.53 mmol, 78%) as a clear oil which crystallized on standing.

m.p. = 38 °C

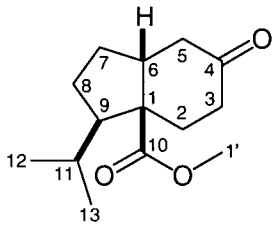
IR (film): ν = 2955, 2872, 1724, 1457, 1433, 1204 cm^{-1}.

^1H NMR (400 MHz): δ = 0.82 (d, 3 H, J = 6.5 Hz), 0.89 (d, 3 H, J = 6.5 Hz), 1.14-1.29 (dddd, 1 H, J = 11.0, 11.0, 10.6, 7.4 Hz), 1.48-1.71 (m, 3 H), 1.75-1.85 (m, 2 H), 1.92-2.02 (dddd, 1 H, J = 7.4, 7.4, 7.4, 6.7 Hz), 2.19-2.27 (m, 3 H), 2.42-2.57 (m, 2 H), 2.80-2.90 (dddd, 1 H, 10.6, 6.7, 6.7, 6.7 Hz), 3.70 (s, 3 H).

^{13}C NMR (100 MHz): δ = 21.1 (−ve), 22.7 (−ve), 28.2 (+ve), 29.8 (−ve), 30.7 (+ve), 32.1 (+ve), 36.7 (+ve), 42.3 (−ve), 43.3 (+ve), 51.7 (−ve), 54.2 (+ve), 57.5 (−ve), 176.6 (+ve), 212.6 (+ve).

Exact mass calculated for $C_{14}H_{22}O_3$: 238.1569; found 238.1568.

Table 4.12: NMR data for methyl (1*R**,6*R**,9*R**)-9-isopropyl-4-oxobicyclo[4.3.0]nonane-1-carboxylate (**256**)



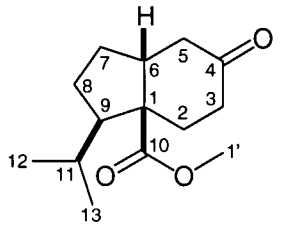
Carbon No.	^{13}C δ (ppm)[a]	^{1}H δ (ppm) (mult; *J* (Hz))[b,c,d]	HMBC Correlations[e]
1	54.2		H-2a, H-2b, H-6, H-7b
2	36.7	H-2a: part of the m at 2.19-2.27	H-3a, H-3b
		H-2b: part of the m at 2.19-2.27	
3	30.7	H-3a: part of the m at 1.75-1.85	
		H-3b: part of the m at 2.42-2.57	
4	212.6		H-3a, H-5a, H-5b, H-6
5	43.3	H-5a: part of the m at 2.19-2.27	H-6
		H-5b: part of the m at 2.42-2.57	
6	42.3	H-6: 2.80-2.90 (dddd, *J* = 10.6, 6.7, 6.7, 6.7)	H-5a, H-5b, H-7a, H-7b, H-8b
7	32.1	H-7a: 1.14-1.29 (dddd, *J* = 11.0, 11.0, 10.6, 7.4)	H-5b, H-6, H-8b
		H-7b: 1.92-2.02 (dddd, *J* = 7.4, 7.4, 7.4, 6.7)	
8	28.2	H-8a: part of the m at 1.48-1.71	H-7b, H-9, H-11
		H-8b: part of the m at 1.75-1.85	
9	57.5	H-9: part of the m at 1.48-1.71	H-7b, H-8b, H-12, H-13
10	176.6		H-2a, H-2b, H-3a, H-3b, H-5b, H-6, H-8b
11	29.8	H-11: part of the m at 1.48-1.71	H-8a, H-9, H-12, H-13
12	21.1	H-12: 0.82 (d, *J* = 6.5)	H-9, H-11, H-13
13	22.7	H-13: 0.89 (d, *J* = 6.5)	H-9, H-11, H-12
1'	51.7	H-1': 3.70 (s)	

[a] Recorded at 100 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC and JMOD data.

[d] Methylene protons are designated H-Xa and H-Xb arbitrarily.

[e] Only those correlations which could be unambiguously assigned are recorded.

Table 4.13: NMR data for methyl (1*R**,6*R**,9*R**)-9-isopropyl-4-oxobicyclo[4.3.0]nonane-1-carboxylate (**256**)



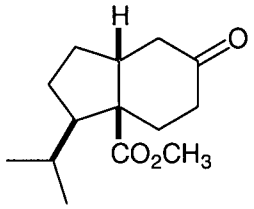
Proton No.	^{1}H δ (ppm) (mult; *J* (Hz))[a,b,c]	COSY Correlations[d]
H-2a	part of the m at 2.19-2.27	H-3a, H-3b
H-2b	part of the m at 2.19-2.27	H-3a, H-3b
H-3a	part of the m at 1.75-1.85	H-2a, H-2b, H-3b
H-3b	part of the m at 2.42-2.57	H-2a, H-2b, H-3a
H-5a	part of the m at 2.19-2.27	H-5b, H-6
H-5b	part of the m at 2.42-2.57	H-5a, H-6
H-6	2.80-2.90 (dddd, *J* = 10.6, 6.7, 6.7, 6.7)	H-5a, H-5b, H-7a, H-7b
H-7a	1.14-1.29 (dddd, *J* = 11.0, 11.0, 10.6, 7.4)	H-6, H-7b, H-8a
H-7b	1.92-2.02 (dddd, *J* = 7.4, 7.4, 7.4, 6.7)	H-6, H-7a, H-8a, H-8b
H-8a	part of the m at 1.48-1.71	H-7a, H-7b, H-8b
H-8b	part of the m at 1.75-1.85	H-7a, H-8b, H-9
H-9	part of the m at 1.48-1.71	
H-11	part of the m at 1.48-1.71	H-12, H-13
H-12	0.82 (d, *J* = 6.5)	H-11
H-13	0.89 (d, *J* = 6.5)	H-11
H-1'	3.70 (s)	

[a] Recorded at 400 MHz. [b] Assignments based on HMQC and JMOD data.

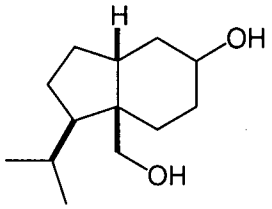
[c] Methylene protons are designated H-Xa and H-Xb arbitrarily.

[d] Only those correlations which could be unambiguously assigned are recorded.

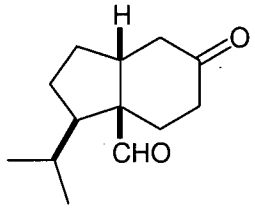
(1*R,6*S**,9*R**)-9-Isopropyl-4-oxobicyclo[4.3.0]nonane-1-carbaldehyde (258)**



256



257



258

To a cold (0 °C), stirred solution of keto ester **256** (40 mg, 0.17 mmol) in Et_2O (5 mL) was added, via a syringe, DIBAL-H (1.0 M in hexanes, 0.59 mL, 0.59 mmol). The reaction mixture was stirred at this temperature for 1 h. $MgSO_4 \bullet 7H_2O$ (200 mg, 0.81 mmol) was added and the resulting heterogeneous mixture was stirred vigorously for 1 h. The mixture was filtered through a sintered glass funnel and the funnel was rinsed with Et_2O. The eluate was concentrated and the residual oil was purified by flash column chromatography (5 g of silica gel, 2:1 Et_2O-petroleum ether) to provide a mixture of alcohols **257**.

The acquired mixture of alcohols **257** was dissolved in DCM (5 mL). To the resulting solution were added, sequentially, NMO (30 mg, 2.5 mmol) in one portion and TPAP (10 mg, 0.03 mmol) in one portion. The reaction mixture was allowed to stir at r.t. for 2 h. The mixture was filtered through a pad of silica gel (1 g) and the silica gel was rinsed with Et_2O. The collected eluate was concentrated and the residual oil was purified by flash column chromatography (15 g silica gel, 1:1 petroleum ether-Et_2O) to yield keto aldehyde **258** (25 mg, 0.12 mmol, 72%) as a clear oil.

Keto aldehyde **258** exhibited:

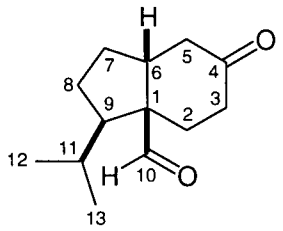
IR (film): ν = 2962, 1721, 1709, 1474, 737 cm^{-1}.

^1H NMR (400 MHz): δ = 0.90 (d, 3 H, J = 6.3 Hz), 0.93 (d, 3 H. J = 6.3 Hz), 1.21-1.33 (dddd, 1 H, J = 12.2, 12.2, 10.2, 6.4 Hz), 1.36-1.49 (dddd, 1 H, J = 12.2, 12.2, 12.2, 7.1 Hz), 1.66-1.82 (m, 3 H), 1.92-2.01 (m, 1 H), 2.01-1.11 (m, 1 H), 2.22-2.30 (m, 2 H), 2.26-2.33 (dd, 1 H, J = 15.9, 6.8 Hz), 2.37-2.44 (dd, 1 H, J = 15.9, 5.9 Hz), 2.41-2.49 (ddd, 1 H, J = 14.0, 7.7, 5.5 Hz), 2.60-2.71 (dddd, 1 H, J = 10.4, 6.8, 6.4, 5.9 Hz), 9.71 (s, 1 H).

^{13}C NMR (100 MHz): δ = 22.4 (−ve), 22.4 (−ve), 27.2 (+ve), 29.0 (−ve), 30.3 (+ve), 32.7 (+ve), 35.5 (+ve), 39.1 (−ve), 42.7 (+ve), 56.3 (+ve), 57.5 (−ve), 203.5 (−ve), 212.0 (+ve).

Exact mass calculated for $C_{13}H_{20}O_2$: 208.1463; found 208.1461.

Table 4.14: NMR data for (1*R**,6*S**,9*R**)-9-isopropyl-4-oxobicyclo[4.3.0]nonane-1-carbaldehyde (**258**)



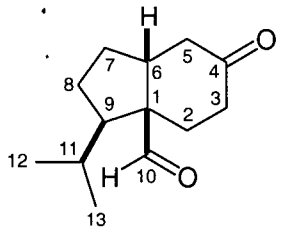
Carbon No.	^{13}C δ (ppm)[a]	^{1}H δ (ppm) (mult; *J* (Hz))[b,c,d]	HMBC Correlations[e]
1	56.3		H-2b, H-3a, H-3b, H-7b, H-8b, H-10
2	27.2	H-2a: part of the m at 1.66-1.82	H-3a, H-3b, H-10
		H-2b: 2.41-2.49 (ddd, *J* = 14.0, 7.7, 5.5)	
3	35.5	H-3a: part of the m at 2.22-2.30	H-2a, H-2b
		H-3b: part of the m at 2.22-2.30	
4	212.0		H-2a, H-2b, H-5a, H-5b, H6
5	42.7	H-5a: 2.26-2.33 (dd, *J* = 15.9, 6.8)	
		H-5b: 2.37-2.44 (dd, *J* = 15.9, 5.9)	
6	39.1	H-6: 2.60-2.71 (dddd, *J* = 10.4, 6.8, 6.4, 5.9)	H-5a, H-5b, H-8b
7	32.7	H-7a: 1.21-1.33 (dddd, *J* = 12.2, 12.2, 10.2, 6.4)	H-5a, H-5b, H-8a, H-8b
		H-7b: 2.01-2.11 (m)	
8	30.3	H-8a: 1.36-1.49 (dddd, *J* = 12.2, 12.2, 12.2, 7.1)	H-7a, H-7b
		H-8b: 1.92-2.01 (m)	
9	57.5	H-9: part of the m at 1.66-1.82	H-7b, H-8a, H-12, H-13
10	203.7	H-10: 9.71 (s)	H-2a, H-2b, H-6, H-9
11	29.0	H-11: part of the m at 1.66-1.82	H-8a, H-12, H-13
12	22.4	H-12: 0.90 (d, *J* = 6.3)	H-13
13	22.4	H-13: 0.93 (d, *J* = 6.3)	H-13

[a] Recorded at 100 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC and JMOD data.

[d] Methylene protons are designated H-Xa and H-Xb arbitrarily.

[e] Only those correlations which could be unambiguously assigned are recorded.

Table 4.15: NMR data for (1*R**,6*S**,9*R**)-9-isopropyl-4-oxobicyclo[4.3.0]nonane-1-carbaldehyde (**258**)



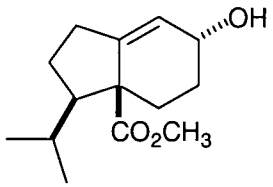
Proton No	^{1}H δ (ppm) (mult; *J* (Hz))[a,b,c]	COSY Correlations[d]
H-2a	part of the m at 1.66-1.82	H-2b, H-3a, H-3b
H-2b	2.41-2.49 (ddd, *J* = 14.0, 7.7, 5.5)	H-2a, H-3a, H-3b
H-3a	part of the m at 2.22-2.30	H-2a, H-2b, H-3b
H-3b	part of the m at 2.22-2.30	H-2a, H-2b, H-3a
H-5a	2.26-2.33 (dd, *J* = 15.9, 6.8)	H-5b, H-6
H-5b	2.37-2.44 (dd, *J* = 15.9, 5.9)	H-5a, H-6
H-6	2.60-2.71 (dddd, *J* = 10.4, 6.8, 6.4, 5.9)	H-5a, H-5b, H-7a, H-7b
H-7a	1.21-1.33 (dddd, *J* = 12.2, 12.2, 10.2, 6.4)	H-6, H-7b
H-7b	2.01-2.11 (m)	H-6, H-7a
H-8a	1.36-1.49 (dddd, *J* = 12.2, 12.2, 12.2, 7.1)	H-8b, H-9
H-8b	1.92-2.01 (m)	H-8a, H-9
H-9	part of the m at 1.66-1.82	H-8a, H-8b
H-10	9.71 (s)	
H-11	part of the m at 1.66-1.82	H-12, H-13
H-12	0.90 (d, *J* = 6.3)	H-11
H-13	0.93 (d, *J* = 6.3)	H-11

[a] Recorded at 400 MHz. [b] Assignments based on HMQC and JMOD data.

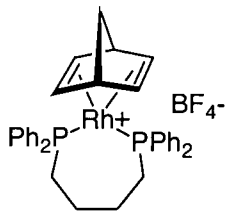
[c] Methylene protons are designated H-Xa and H-Xb arbitrarily.

[d] Only those correlations which could be unambiguously assigned are recorded.

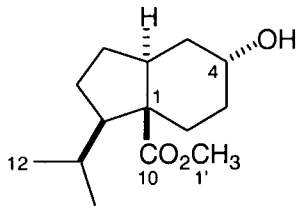
Methyl (1*R,4*R**,6*S**,9*R**)-4-hydroxy-9-isopropylbicyclo[4.3.0]nonane-1-carboxylate (250)**



251



Brown's catalyst



250

To a solution of alcohol **251** (336 mg, 1.4 mmol) in DCM (35 mL) at r.t. was added Brown's catalyst (100 mg, 0.14 mmol). The mixture was placed in a high pressure hydrogenation apparatus and purged with H_2 (g) three times at high pressure (800 psi). The hydrogenation vessel was pressurized to 800 psi and the reaction mixture was stirred for 24 h. After this time the hydrogenation chamber was vented to the atmosphere. The reaction mixture was filtered through a pad of silica gel (5 g) and the silica gel was rinsed with Et_2O. The collected eluate was concentrated and the residual oil was purified by flash column chromatography (10 g of silica gel, 1:1 petroleum ether-Et_2O) to afford alcohol **250** (315 mg, 1.3 mmol, 94%) as a clear oil.

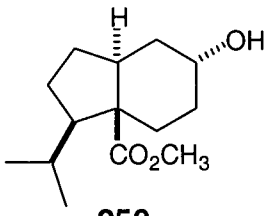
IR (film): ν = 3404, 1723, 1445, 1192, 1006 cm^{-1}.

^1H NMR (400 MHz): δ = 0.82 (d, 3 H, J = 6.5 Hz, Me-12 or Me-13), 0.99 (d, 3 H, J = 6.4 Hz, Me-12 or Me-13), 1.20-1.94 (series of m, 12 H), 2.09-2.20 (dddd, 1 H, J = 12.4, 12.4, 9.0, 3.0 Hz), 2.40-2.47 (ddd, 1 H, J = 12.1, 3.1, 3.1 Hz), 3.63 (s, 3 H, Me-1'), 4.02-4.10 (m, 1 H, H-4).

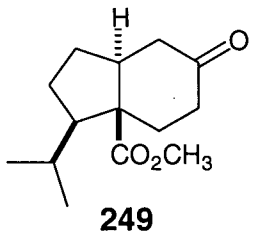
^{13}C NMR (100 MHz): δ = 22.1 (−ve, C-12 or C-13), 22.8 (−ve, C-12 or C-13), 26.8 (+ve), 28.6 (+ve), 31.1 (+ve), 31.6 (+ve), 32.0 (−ve), 34.9 (+ve), 43.5 (−ve), 50.7 (−ve), 57.2 (+ve, C-1), 58.1 (−ve), 66.3 (−ve), 174.8 (+ve, C-10).

Exact mass calculated for $C_{14}H_{24}O_3$: 240.1725; found 240.1722.

Methyl (1*R,6*S**,9*R**)-9-isopropyl-4-oxobicyclo[4.3.0]nonane-1-carboxylate (249)**



250



249

Alcohol **250** was oxidized to ketone **249** using the method developed by Ley.[88] Thus, to a stirred solution of alcohol **250** (208 mg, 0.87 mmol) in DCM (10 mL) at r.t. was added, sequentially, TPAP (15 mg, 0.4 mmol) in one portion and NMO (112 mg, 0.95 mmol) in one portion. The mixture was allowed to stir overnight. The reaction mixture was filtered through a pad of silica gel (5 g) and the silica gel was rinsed with Et_2O. The collected eluate was concentrated and the residual oil was purified by flash column chromatography (10 g of silica gel, 2:1 petroleum ether-Et_2O) to yield ketone **249** (184 mg, 77 mmol, 88%) as a clear oil.

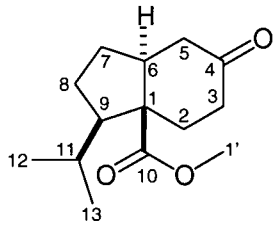
IR (film): ν = 2951, 1720, 1456, 1179, 1000, 738 cm^{-1}.

^1H NMR (400 MHz): δ = 0.85 (d, 3 H, J = 6.1 Hz), 0.98 (d, 3 H, J = 6.1 Hz), 1.36-1.50 (m, 2 H), 1.45-1.55 (ddd, 1 H, J = 13.1, 12.6, 5.8 Hz), 1.61-1.72 (m, 2 H), 1.79-1.92 (dddd, 1 H, J = 11.9, 11.9, 11.9, 4.4 Hz), 1.98-2.16 (m, 2 H), 2.28-2.40 (m, 3 H), 2.40-2.51 (ddd, 1 H, J = 17.0, 12.6, 6.8 Hz), 2.75-2.83 (ddd, 1 H, J = 13.1, 6.8, 1.8 Hz), 3.72 (s, 3 H).

^{13}C NMR (100 MHz): δ = 22.2 (−ve), 22.6 (−ve), 26.8 (+ve), 30.1 (+ve), 31.9 (−ve), 34.3 (+ve), 38.6 (+ve), 43.7 (+ve), 50.4 (−ve), 51.2 (−ve), 56.1 (+ve), 57.3 (−ve), 173.9 (+ve), 210.9 (+ve).

Exact mass calculated for $C_{14}H_{22}O_3$: 238.1569; found 238.1567.

Table 4.16: NMR data for methyl (1*R**,6*S**,9*R**)-9-isopropyl-4-oxobicyclo[4.3.0]nonane-1-carboxylate (**249**)



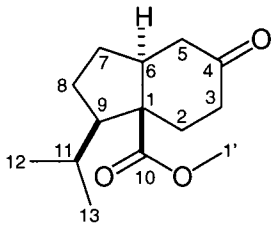
Carbon No.	^{13}C δ (ppm)[a]	^{1}H δ (ppm) (mult; *J* (Hz))[b,c,d]	HMBC Correlations[e]
1	56.1		H-1', H-2a, H-2b, H-3a, H-3b
2	34.3	H-2a: 1.45-1.55 (dddd, *J* = 13.1, 12.6, 5.8)	H-3a, H-3b, H-6, H-9
		H-2b: 2.75-2.83 (ddd, *J* = 13.1, 6.8, 1.8)	
3	38.6	H-3a: 2.28-2.40 (ddd, *J* = 17.0, 5.8, 1.8)	H-2a, H-2b
		H-3b: 2.40-2.51 (ddd, *J* = 17.0, 12.6, 6.8)	
4	210.9		H-2a, H-2b, H-3a, H-3b, H-6
5	43.7	H-5a: part of the m at 2.28-2.40	H-7
		H-5b: part of the m at 2.28-2.40	
6	50.4	H-6: part of the m at 1.98-2.16	H-2b, H-5a, H-5b, H-7b
7	26.8	H-7a: part of the m at 1.61-1.72	H-5b, H-6, H-8b
		H-7b: 1.79-1.92 (dddd, *J* = 11.9, 11.9, 11.9, 4.4)	
8	30.1	H-8a: part of the m at 1.61-1.72	H-7a, H-7b
		H-8b: part of the m at 1.98-2.16	
9	57.3	H-9: part of the m at 1.36-1.50	H-12, H-13
10	173.9		H-1', H-3a, H-3b, H-6, H-11, H-12
11	31.9	H-11: part of the m at 1.36-1.50	H-8a, H-12, H-13
12	22.2	H-12: 0.98 (d, *J* = 6.1)	H-9, H-11, H-13
13	22.6	H-13: 0.85 (d, *J* = 6.1)	H-9, H-11, H-12
1'	51.2	H-1': 3.72 (s)	

[a] Recorded at 100 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC and JMOD data.

[d] Methylene protons are designated H-Xa and H-Xb arbitrarily.

[e] Only those correlations which could be unambiguously assigned are recorded.

Table 4.17: NMR data for methyl (1*R**,6*S**,9*R**)-9-isopropyl-4-oxobicyclo[4.3.0]nonane-1-carboxylate (**249**)



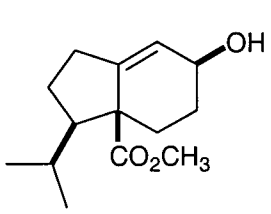
Proton No	^{1}H δ (ppm) (mult; *J* (Hz))[a,b,c]	COSY Correlations[d]
H-2a	1.45-1.55 (dddd, *J* = 13.1, 12.6, 5.8)	H-2b, H-3a, H-3b
H-2b	2.75-2.83 (ddd, *J* = 13.1, 6.8, 1.8)	H-2a, H-3a, H-3b
H-3a	2.28-2.40 (ddd, *J* = 17.0, 5.8, 1.8)	H-2a, H-2b, H-3b
H-3b	2.40-2.51 (ddd, *J* = 17.0, 12.6, 6.8)	H-2a, H-2b, H-3a
H-5a	part of the m at 2.28-2.40	H-5b, H-6
H-5b	part of the m at 2.28-2.40	H-5a, H-6
H-6	part of the m at 1.98-2.16	H-5a, H-5b, H-7a, H-7a
H-7a	part of the m at 1.61-1.72	H-6, H-7b, H-8b,
H-7b	1.79-1.92 (dddd, *J* = 11.9, 11.9, 11.9, 4.4)	H-6, H-7a, H-8a, H-8b
H-8a	part of the m at 1.61-1.72	H-7b, H-9
H-8b	part of the m at 1.98-2.16	H-7a, H-7b, H-9
H-9	part of the m at 1.36-1.50	H-8a, H-8b
H-11	part of the m at 1.36-1.50	H-12, H-13
H-12	0.98 (d, *J* = 6.1)	H-11
H-13	0.85 (d, *J* = 6.1)	H-11
H-1'	3.72 (s)	

[a] Recorded at 400 MHz. [b] Assignments based on HMQC and JMOD data.

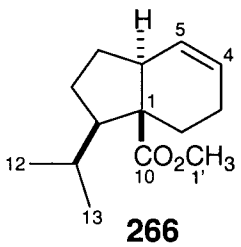
[c] Methylene protons are designated H-Xa and H-Xb arbitrarily.

[d] Only those correlations which could be unambiguously assigned are recorded.

Methyl (1*S,6*S**,9*R**)-9-isopropylbicyclo[4.3.0]non-4-ene-1-carboxylate (266)**



252



266

Alkene **266** was prepared from alcohol **252** using the method developed by Myers.[133] Thus, to a cold (–30 °C), stirred solution of Ph_3P (8.18 g, 31.2 mmol) in NMM (92 mL) was added drop-wise, via a syringe, DEAD (5.58 mL, 31.2 mmol). The resulting solution was allowed to stir for 5 min. A cold (–30 °C) solution of alcohol **252** (6.19 g, 26 mmol) in NMM (15 mL) was added via a cannula and the resulting reaction mixture was allowed to stir for 10 min. Solid NBSH (6.27 g, 31.2 mmol) was added in one portion and the reaction mixture was stirred for 1 h. TLC analysis of the mixture indicated that the starting material had been consumed. The reaction mixture was allowed to warm up to r.t. over 1 h. Et_2O (500 mL) and H_2O (500 mL) were added and the layers were allowed to separate. The organic layer was washed with H_2O (500 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (300 g of silica gel, 9:1 petroleum ether-Et_2O) to provide alkene **266** (3.65 g, 16.4 mmol, 63%) as a clear oil.

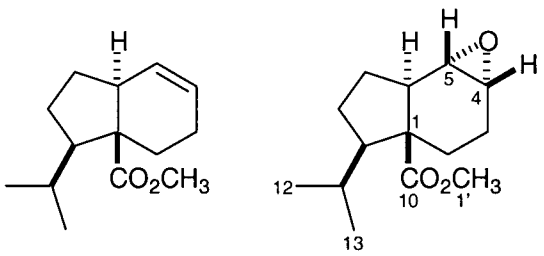
IR (film): ν = 2948, 1724, 1433, 1163, 685 cm^{-1}.

^1H NMR (400 MHz): δ = 0.81 (d, 3 H, J = 6.4 Hz, Me-12 or Me-13), 0.99 (d, 3 H, J = 6.4 Hz, Me-12 or Me-13), 1.27-1.60 (m, 4 H), 1.66-1.78 (m, 1 H), 1.87-2.02 (m, 2 H), 2.04-2.17 (m, 1 H), 2.20-2.34 (m, 1 H), 2.41-2.51 (m, 1 H), 2.60-2.69 (dd, 1 H, J = 12.9, 7.8 Hz), 3.58 (s, 3 H, Me-1'), 5.40-5.49 (dddd, 1 H, J = 9.8, 3.3, 3.3, 3.3 Hz, H-4 or H-5), 5.68-5.75 (dddd, 1 H, J = 9.8, 2.2, 2.2, 2.2 Hz, H-4 or H-5).

^{13}C NMR (100 MHz): δ = 22.3 (C-12 or C-13), 22.7 (C-12 or C-13), 25.0, 26.0, 29.5, 32.1, 33.9, 48.6, 50.6, 56.6 (C-1), 56.8, 126.6 (C-4 or C-5), 129.4 (C-4 or C-5), 174.8 (C-10).

Exact mass calculated for $C_{14}H_{22}O_2$: 222.1620; found: 222.1627.

Methyl (1S*,4R*,5S*,6R*,9R*)-9-isopropyl-4,5-epoxybicyclo[4.3.0]nonane-1-carboxylate (270)



266 **270**

To a cold (–78 °C), stirred solution of freshly distilled DMDO (~0.09-0.11 M in acetone, 300 mL, ~30 mmol) was added a solution of alkene **266** (3.20 g, 14.4 mmol) in acetone (40 mL). The solution was allowed to warm to r.t. overnight. Et_2O (300 mL) and H_2O (300 mL) were added and the layers were allowed to separate. The organic layer was washed with sat. aq $NaHCO_3$ (300 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (200 g of silica gel, 9:1 petroleum ether-Et_2O) to provide epoxide **270** (1.96 g, 8.2 mmol, 57%) as a clear oil.

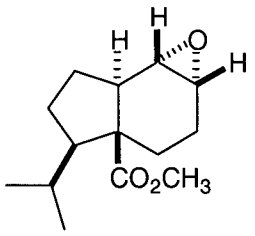
IR (film): ν = 2954, 1725, 1455, 1174, 834 cm^{-1}.

^1H NMR (400 MHz): δ = 0.80 (d, 3 H, J = 6.4 Hz, Me-12 or Me-13), 1.01 (d, 3 H, J = 6.3 Hz, Me-12 or Me-13), 1.08-1.18 (ddd, 1 H, J = 12.9, 11.7, 6.6 Hz), 1.23-1.44 (m, 3 H), 1.57-1.66 (ddd, 1 H, J = 11.2, 9.1, 1.6 Hz), 1.72-1.84 (dddd, 1 H, J = 15.0, 11.0, 7.3, 3.4 Hz), 1.85-2.12 (m, 4 H), 2.29-2.38 (dd, 1 H, J = 13.0, 7.3 Hz), 2.97-3.02 (dd, 1 H, J = 4.1, 4 Hz. H-4 or H-5), 3.16-3.20 (dd, 1 H, J = 4.1, 2.1 Hz, H-4 or H-5), 5.35 (s, 3 H, Me-1').

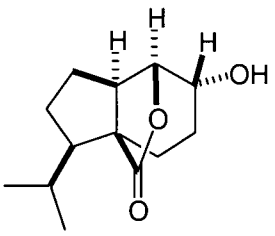
^{13}C NMR (100 MHz): δ = 22.4, 22.6, 22.8, 24.6, 28.8, 31.1, 31.6, 51.0 (C-1), 51.1 (2 C), 55.6 (2 C), 55.8, 174.4 (C-10).

Exact mass calculated for $C_{14}H_{22}O_3$: 238.1569; found: 238.1574.

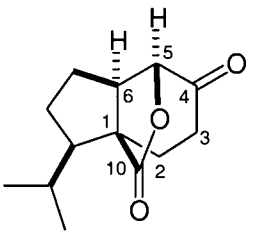
(1*S,5*R**,6*R**,9*R**)-9-Isopropyl-4-oxobicyclo[4.3.0]nonane-1,5-carbolactone (272)**



270



271



272

To a cold (0 °C), stirred suspension of CuBr•DMS (1.79 g, 8.72 mmol) in Et_2O (100 mL) was added, via a syringe, MeLi (12.5 mL, 1.4 M in Et_2O, 17.4 mmol). The resulting mixture was allowed to stir for 20 min. A solution of epoxide **270** (1.73 g, 7.27 mmol) in Et_2O (25 mL) at r.t. was transferred to the reaction vessel via a cannula. The resulting mixture was allowed to cool to 0 °C over 15 min. Neat BF_3•Et_2O (1.14 g, 7.99 mmol) was added drop-wise via a syringe. The reaction mixture was allowed to stir for 10 min. TLC analysis of the reaction mixture indicated that the starting material had been consumed. Sat. aq NH_4Cl (50 mL) was added and the layers were separated. The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and concentrated to provide crude hydroxy lactone **271**.

Hydroxy lactone **271** was converted to keto lactone **272** using the method developed by Ley.[88] Thus, to a stirred solution of crude hydroxy lactone **271** in DCM (100 mL) at r.t. was added, sequentially, TPAP (255 mg, 0.73 mmol) in one portion and NMO (1.02 g, 8.73 mmol) in one portion. The resulting reaction mixture was allowed to stir overnight. The reaction mixture was filtered through a pad of silica gel (5 g) and the silica gel was rinsed with Et_2O. The collected eluate was concentrated and the residual oil was purified by flash column chromatography (100 g of silica gel, 1:1 petroleum ether-Et_2O) to provide keto lactone **272** (1.15 g, 5.18 mmol, 71%) as a clear oil which crystallized on standing.

m.p. = 64-66 °C

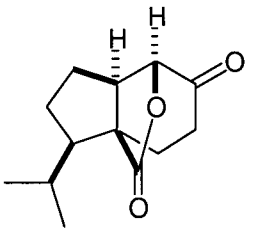
IR (film): ν = 2959, 2872, 1790, 1742, 1456, 1201, 1088, 975 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.86 (d, 3 H, J = 6.7 Hz, Me-12 or Me-13), 1.05 (d, 3 H, J = 6.6 Hz, Me-12 or Me-13), 1.45-1.66 (m, 3 H), 1.66-1.76 (ddd, 1 H, J = 12.7, 11.5, 6.9 Hz, H-2α), 1.90-2.00 (ddd, 1 H, 14.5, 9.6, 5.0 Hz), 2.00-2.08 (m, 1 H), 2.17-2.28 (m, 1 H)2.32-2.38 (dd, 1 H, J = 9, 9 Hz, H-6), 2.36-2.45 (dd, 1 H, J = 16.5, 6.9 Hz, H-3α), 2.47-2.55 (dd, 1 H, J = 12.7, 9.1 Hz, H-2β), 2.59-2.69 (ddd, 1 H, J = 16.5, 11.5, 9.1 Hz, H-3β), 4.35 (s, 1 H, H-5).

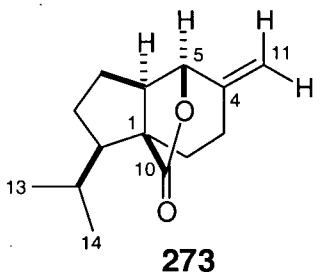
^{13}C NMR (100 MHz): δ = 22.9, 23.1, 23.8, 29.4, 30.0, 31.0, 33.8, 52.7, 55.3 (C-1), 55.9, 83.8 (C-5), 177.1 (C-10), 204.5 (C-4).

Exact mass calculated for $C_{13}H_{18}O_3$: 222.1256; found: 222.1255.

(1S*,5R*,6R*,9R*)-9-Isopropyl-4-methylenebicyclo[4.3.0]nonane-1,5-carbolactone (273)



272



273

To a cold (0 °C), stirred suspension of methyltriphenylphosphonium bromide (926 mg, 2.59 mmol) in THF (10 mL) was added drop-wise, via a syringe, *n*-BuLi (1.62 mL, 1.6 M in hexanes, 2.59 mmol) and the resulting mixture was allowed to stir for 30 minutes. The reaction mixture was then cooled to (–78 °C). A solution of keto lactone **272** (192 mg, 0.87 mmol) in THF (1 mL) was transferred to the reaction vessel via a cannula and the reaction mixture was allowed to warm to r.t. overnight. TLC analysis of the reaction mixture indicated that the starting material had been consumed. Et_2O (10 mL) and H_2O (10 mL) were added and the layers were separated. The organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (10 g of silica gel, 9:1 petroleum ether-Et_2O) to afford alkene **273** (160 mg, 0.72 mmol, 83%) as a clear oil.

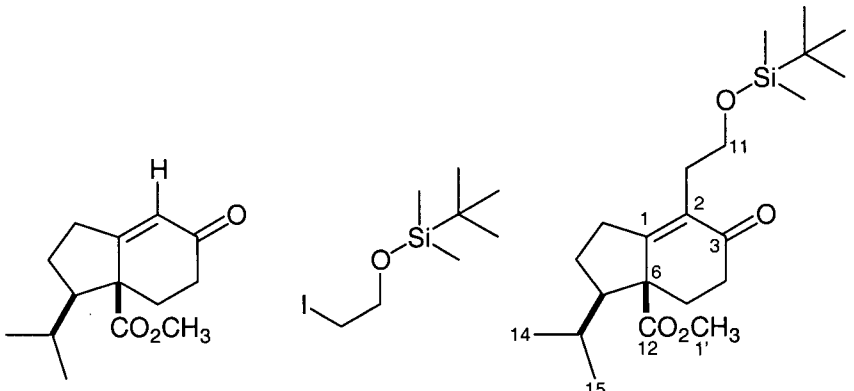
IR (film): ν = 2960, 1770, 1475, 1456, 1203, 1094, 956, cm^{-1}.

^1H NMR (400 MHz): δ = 0.87 (d, 3 H, J = 6.9 Hz, Me-13 or Me-14), 1.07 (d, 3 H, J = 6.9 Hz, Me-13 or Me-14), 1.39-1.65 (m, 4 H), 1.82-2.01 (m, 2 H), 2.05-2.12 (dd, 1 H, J = 9.6 Hz), 2.17-2.29 (m, 1 H), 2.32-2.47 (m, 3 H), 4.69 (s, 1 H, H-5), 4.79 (s, 1 H, H-11), 4.86 (s, 1 H, H-11).

^{13}C NMR (100 MHz): δ = 23.1, 23.4, 24.3, 27.3, 29.8, 30.4, 32.3, 53.6, 56.3 (C-1), 57.2, 83.7 (C-5), 109.7 (C-11), 144.5 (C-4), 178.6 (C-10).

Exact mass calculated for $C_{14}H_{12}O_2$: 220.1463; found: 220.1465.

Methyl (6*S,7*R**)-7-isopropyl-3-oxo-2-[2-(*tert*-butyldimethylsiloxy)ethyl]bicyclo [4.3.0]non-1-ene-6-carboxylate (293)**



197 **292** **293**

To a stirred suspension of NaH (70 mg of a 60% suspension in mineral oil, 1.75 mmol) in DME (10 mL) at r.t. was added, via a cannula, a solution of enone **197** (472 mg, 2.00 mmol) in DME (5 mL). The resulting reaction mixture was allowed to stir for 1 h. During this time the mixture became dark purple in colour. A solution of iodide **292** (858 mg, 3.00 mmol) in DME (5 mL) was transferred to the reaction vessel via a cannula. The reaction mixture was allowed to stir overnight. Sat. aq NH_4Cl (10 mL) was added and the resulting mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified using flash column chromatography (25 g of silica gel, 9:1 petroleum ether-Et_2O) to afford enone **293** (498 mg, 78% based on recovered starting material) as a clear oil. In addition, enone **197** was recovered (91 mg, 19%). Enone **293** exhibited:

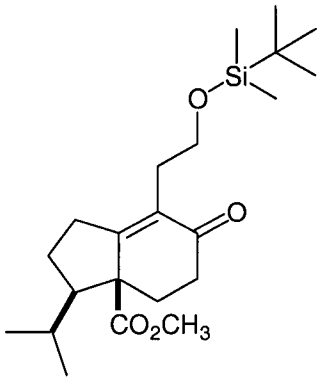
IR (film): ν = 2952, 1729, 1668, 1357, 1100, 837 cm^{-1}.

^1H NMR (400 MHz): δ = −0.04 (s, 3 H, Si-C$\underline{H}_3$), −0.02 (s, 3 H, Si-C$\underline{H}_3$), 0.83 (s, 9 H, Si-C(C$\underline{H}_3$)$_3$), 0.86 (d, 3 H, J = 6.4 Hz, Me-14 or Me-15), 1.02 (d, 3 H, J = 6.4 Hz, Me-14 or Me-15), 1.42-1.58 (m, 2 H), 1.62-1.78 (m, 2 H), 1.91-2.01 (m, 1 H), 2.98-2.37 (ddd, 1 H, J = 18.2, 5.1, 2.3 Hz), 2.37-2.49 (m, 3 H), 2.60-2.75 (m, 1 H), 2.70-2.81 (ddd, 1 H, J = 19.6, 9.1, 1.9 Hz), 2.81-2.88 (ddd, 1 H, J = 12.7, 4.5, 2.5 Hz), 3.50-3.64 (m, 2 H, H-11), 3.65 (s, 3 H, Me-1').

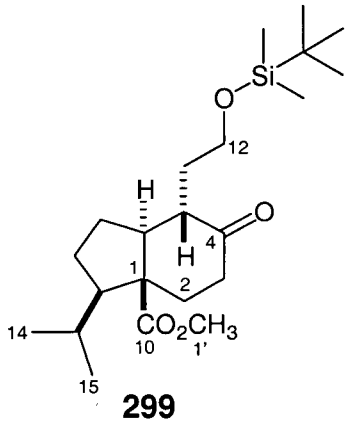
^{13}C NMR (100 MHz): δ = −5.5 (−ve, Si-$\underline{C}H_3$), −5.4 (−ve, Si-$\underline{C}H_3$), 18.2 (+ve, Si-$\underline{C}(CH_3)_3$), 22.0 (−ve, C-14 or C-15), 22.5 (−ve, C-14 or C-15), 25.9 (3 C, −ve, Si-C($\underline{C}H_3)_3$), 27.7 (+ve), 29.8 (+ve), 30.0 (+ve), 30.6 (-ve), 33.6 (+ve), 34.8 (+ve), 51.8 (−ve), 57.1 (+ve, C-6), 58.8 (−ve, C-1'), 61.6 (+ve, C-11), 130.2 (+ve, C-2), 167.9 (+ve, C-1 or C-12), 172.1 (+ve, C-1 or C-12), 198.0 (+ve, C-3).

Exact mass calculated for $C_{22}H_{38}O_4Si$: 394.2539; found: 394.2534.

Methyl (1*S,5*S**,6*S**,9*R**)-9-isopropyl-4-oxo-5-[2-(*tert*-butyldimethylsiloxy)ethyl] bicyclo[4.3.0]nonane-1-carboxylate (299)**



293

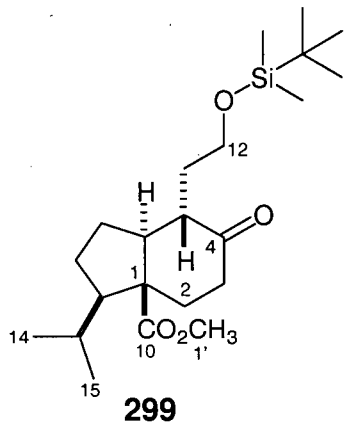


299

The hydrogenation of enone **293** was not a reproducible process. Best results were obtained in small scale reactions with a high load of palladium-on-carbon.

To a solution of enone **293** (115 mg, 0.16 mmol) in EtOH (5 mL) was added palladium on carbon (60 mg, 10% by weight) and the reaction was allowed to stir under hydrogen at one atmosphere. After 1 h TLC analysis of the mixture indicated that the starting material had been consumed. The reaction mixture was filtered through a pad of silica (1 g) and the silica gel was rinsed with Et_2O. The combined filtrated was washed with H_2O (2 x 10 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated. The residual oil was dissolved in MeOH (5 mL) and NaOMe (20 mg, 0.37 mmol) was added in one portion. The resulting reaction mixture was stirred overnight. H_2O (10 mL) and Et_2O were added and the layers were separated. The organic layer was washed with brine (5 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography to provide ketone **299** (89 mg, 77%) as a clear oil.

Ketone **299** exhibited:



299

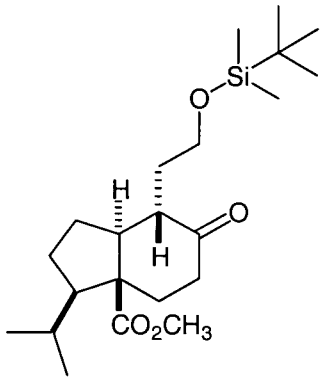
IR (film): ν = 2954, 1724, 1712, 1092, 836 cm^{-1}.

^1H NMR (400 MHz): δ = −0.02 (s, 3 H, Si-C$\underline{H}_3$), −0.01 (s, 3 H, Si-C$\underline{H}_3$), 0.83 (d, 3 H, J = 6.2 Hz, Me-14 or Me-15), 0.85 (s, 9 H, Si-C(C$\underline{H}_3$)$_3$), 0.96 (d, 3 H, J = 6.2 Hz, Me-14 or Me-15), 1.34-1.84 (m, 7 H), 1.84-1.95 (m, 2 H), 1.95-2.05 (m, 1 H), 2.28-2.37 (ddd, 1 H, J = 15.6, 5.3, 2.1 Hz), 2.41-2.54 (m, 2 H), 2.73-2.83 (ddd, 1 H, J = 13.1, 6.7, 2.1 Hz, H-2β), 3.51-3.59 (ddd, 1 H. J = 9.9, 8.0, 6.3 Hz, H-12), 3.64-3.72 (ddd, 1 H, J = 10.1, 7.2, 4.7 Hz, H-12), 3.70 (s, 3 H, Me-1').

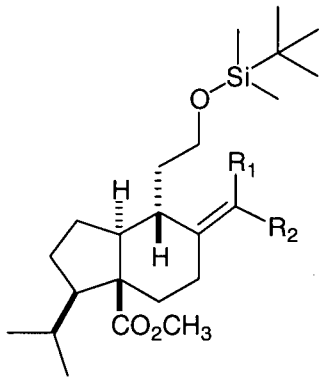
^{13}C NMR (100 MHz): δ = −5.4 (2 C, Si-$\underline{C}H_3$), 18.2 (+ve, Si-$\underline{C}$(CH$_3$)$_3$), 22.1 (−ve, C-14 or C-15), 22.5 (−ve, C-14 or C-15), 25.8 (+ve), 25.9 (3 C, −ve, Si-C($\underline{C}$H$_3$)$_3$), 30.0 (+ve), 30.3 (+ve), 31.9 (−ve), 34.9 (+ve), 39.2 (+ve), 48.1 (−ve), 51.2 (−ve), 55.3 (−ve), 57.0 (+ve, C-1), 57.4 (−ve), 61.2 (+ve, C-12), 174.1 (+ve, C-10), 211.9 (+ve, C-4).

Exact mass calculated for $C_{18}H_{31}O_4Si$ [M − *t*-Bu]$^+$: 339.1992; found: 339.1991.

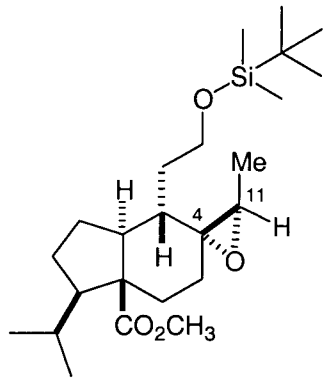
Methyl (1*S,4*R**,5*S**,6*S**,9*R**,11*R**)-4,11-epoxy-4-ethyl-9-isopropyl-5[2-(tert-butyldimethylsiloxy)ethyl]bicyclo[4.3.0]nonane-1-carboxylate (302)**



299



300: R_1 = Me, R_2 = H
301: R_1 = H, R_2 = Me



302

To a cold (0 °C), stirred suspension of ethyltriphenylphosphonium bromide (112 mg, 0.30 mmol) in THF (3 mL) was added BuLi (113 μL, 1.6 M in hexanes, 0.18 mmol) and the resulting reaction mixture was allowed to stir for 30 min. A solution of ketone **299** (60 mg, 0.15 mmol) in THF (2 mL) was transferred to the reaction vessel via a cannula and the reaction mixture was allowed to warm up to r.t. overnight. H_2O (3 mL) and Et_2O (5 mL) were added and the layers were separated. The organic layer was washed with brine (5 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (5 g of silica gel, 9:1 petroleum ether-Et_2O) to afford an inseparable mixture of alkenes **300** and **301** (48 mg, ratio 11:1, 78%) as a clear oil.

To a cold (–78 °C), stirred solution of the acquired mixture of alkenes **300** and **301** in DCM (6 mL) was added, dropwise, via a pipette, a solution of freshly distilled DMDO (1.4 mL, ~0.09-0.11 M, ~0.13-0.15 mmol). The resulting mixture was allowed to stir for 1 h. TLC analysis of the mixture indicated that all the starting material had been consumed. H_2O (5 mL) and Et_2O (10 mL) were added and the layers were separated. The organic layer was washed with brine (5 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (10 g of silica gel, 9:1 petroleum ether-Et_2O) to afford oxirane **302** (45 mg, 89%) as a clear oil. No effort to isolate or characterize the oxirane derived from alkene **301** was made.

Oxirane **302** exhibited:

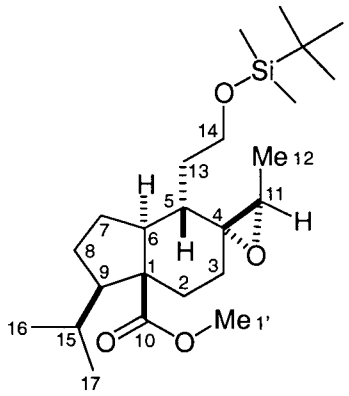
IR (film): ν = 2955, 1723, 1255, 1164, 1095, 836 cm^{-1}.

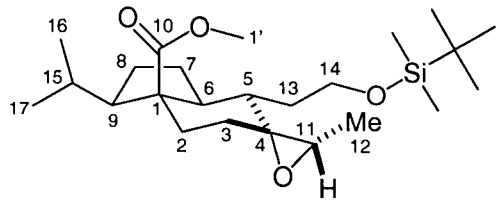
^1H NMR (500 MHz): δ = 0.00 (s, 3 H, Si-C$\underline{H}_3$), 0.01 (s, 3 H, Si-C$\underline{H}_3$), 0.80 (d, 3 H, J = 6.5 Hz), 0.86 (s, 9 H, Si-C(C$\underline{H}_3$)$_3$), 0.89 (d, 3 H, J = 6.5 Hz), 0.90-0.98 (m, 1 H), 1.08 (d, 3 H, J = 5.4 Hz), 1.14-1.28 (m, 1 H), 1.37-1.75 (m, 6 H), 1.76-1.84 (m, 1 H), 1.84-1.92 (m, 1 H), 1.92-2.01 (m, 1 H), 2.05-2.14 (ddd, 1 H, J = 19.7, 10.7, 10.7 Hz), 2.14-2.22 (ddd, 1 H, J = 13.4, 10.3, 10.3 Hz), 2.67-2.72 (q, 1 H, J = 5.4 Hz), 2.70-2.79 (ddd, 1 H, J = 13.7, 9.3, 9.3 Hz), 3.56-3.71 (m, 2 H), 3.65 (s, 3 H).

^{13}C NMR (125 MHz): δ = −5.4 (−ve, Si-$\underline{C}H_3$), −5.3(−ve, Si-$\underline{C}H_3$), 14.0 (−ve), 18.2 (+ve, Si-$\underline{C}$(CH$_3$)$_3$), 21.9 (−ve), 22.6 (−ve), 25.9 (3 C, −ve, Si-C($\underline{C}$H$_3$)$_3$), 27.3 (+ve), 29.0 (+ve), 30.7 (+ve), 31.1 (+ve), 32.0 (−ve), 34.2 (+ve), 34.3 (−ve), 50.8 (−ve), 52.3 (−ve), 55.5 (+ve), 60.0 (−ve), 61.6 (+ve), 61.8 (−ve), 63.4 (+ve), 175.3 (+ve).

Exact mass calculated for $C_{24}H_{44}O_4Si$: 424.3009; found: 424.3007.

Table 4.18: NMR data for Methyl (1*S**,4*R**,5*S**,6*S**,9*R**,11*R**)-4,11-epoxy-4-ethyl-9-isopropyl-5[2-(tert-butyldimethylsiloxy)ethyl]bicyclo[4.3.0]nonane-1-carboxylate (**302**)





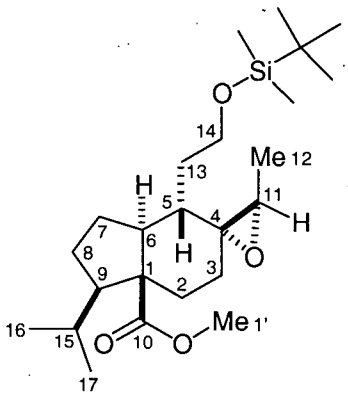
Carbon No.	^{13}C δ (ppm)[a]	^{1}H δ (ppm) (mult; *J* (Hz))[b,c,d]
1	55.5	
2	31.1	H-2a: part of the m at 1.37-1.75 (dd; 13.7, 10.3)
		H-2b: 2.70-2.79 (ddd; 13.7, 9.3, 9.3)
3	29.0	H-3a: 0.90-0.98 (ddd; 13.4, 9.3)
		H-3b: 2.14-2.22 (ddd; 13.4, 10.3, 9.3)
4	63.4	
5	34.3	H-5: part of the m at 1.37-1.75
6	52.3	H-6: 2.05-2.14 (ddd; 19.7, 10.7, 10.7)
7	27.3	H-7a: 1.84-1.92 (m)
		H-7b: part of the m at 1.37-1.75
8	30.7	H-8a: 1.92-2.01 (m)
		H-8b: part of the m at 1.37-1.75
9	60.0	H-9: part of the m at 1.37-1.75
10	175.3	
11	61.8	H-11: 2.67-2.72 (q; 5.4)
12	14.0	H-12: 1.08 (d; 5.4)
13	34.2	H-13a: 1.76-1.84 (m)
		H-13b: part of the m at 1.37-1.75
14	61.6	H-14a: part of the m at 3.56-3.71
		H-14b: part of the m at 3.56-3.71
15	32.0	H-15: 1.14-1.28 (m)
16	21.9	H-16: 0.89 (d; 6.5)
17	22.6	H-17: 0.80 (d; 6.5)
1'	50.8	H-1': 3.65 (s)

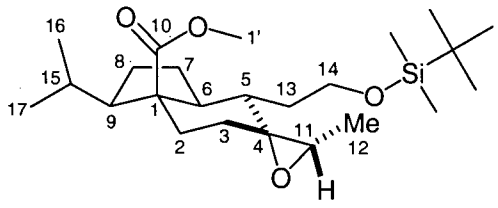
[a] Recorded at 125 MHz. [b] Recorded at 500 MHz.

[c] Assignments based on HMQC and JMOD data.

[d] Methylene protons are designated H-Xa and H-Xb arbitrarily.

Table 4.19: NMR data for Methyl (1*S**,4*R**,5*S**,6*S**,9*R**,11*R**)-4,11-epoxy-4-ethyl-9-isopropyl-5[2-(tert-butyldimethylsiloxy)ethyl]bicyclo[4.3.0]nonane-1-carboxylate (**302**)





Proton No.	^{1}H δ (ppm) (mult; *J* (Hz))[a,b,c]	COSY Correlations[d]	NOE Correlations[d,e]
H-2a	part of the m at 1.37-1.75 (dd; 13.7, 10.3)	H-2b, H-3b	
H-2b	2.70-2.79 (ddd; 13.7, 9.3, 9.3)	H-2a, H-3b, H-3a	H-2a, H-3a
H-3a	0.90-0.98 (dd; 13.4, 9.3)	H-2b, H-3b	
H-3b	2.14-2.22 (ddd; 13.4, 10.3, 9.3)	H-2a, H-2b, H-3a	H-3a
H-5	part of the m at 1.37-1.75		
H-6	2.05-2.14 (ddd; 19.7, 10.7, 10.7)		
H-7a	1.84-1.92 (m)		
H-7b	part of the m at 1.37-1.75		
H-8a	1.92-2.01 (m)		
H-8b	part of the m at 1.37-1.75		
H-9	part of the m at 1.37-1.75		
H-11	2.67-2.72 (q; 5.4)	H-12	H-3a
H-12	1.08 (d; 5.4)	H-11	H-11, H-1'
H-13a	1.76-1.84 (m)	H-13b, H-14a, H-14b	
H-13b	part of the m at 1.37-1.75	H-13a, H-14a, H-14b	
H-14a	part of the m at 3.56-3.71	H-13a, H-13b, H-14b	
H-14b	part of the m at 3.56-3.71	H-13a, H-13b, H-14a	
H-15	1.14-1.28 (m)	H-16, H-17	
H-16	0.89 (d; 6.5)	H-15	
H-17	0.80 (d; 6.5)	H-15	
H-1'	3.65 (s)		

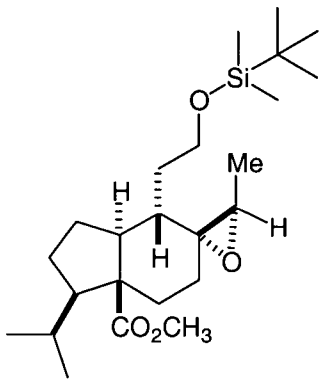
[a] Recorded at 500 MHz. [b] Assignments based on HMQC and JMOD data.

[c] Methylene protons are designated H-Xa and H-Xb arbitrarily.

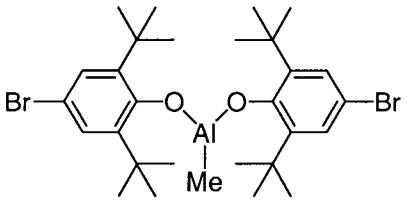
[d] Only those correlations which could be unambiguously assigned are recorded.

[e] Recorded as 1D selective NOE difference at 400 MHz.

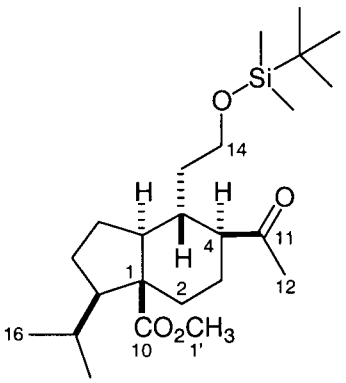
Methyl (1*S,4*S**,5*S**,6*S**,9*R**)-4-acetyl-9-isopropyl-5-[2-(*tert*-butyldimethyl siloxy)ethyl]bicyclo[4.3.0]nonane-1-carboxylate (304)**



302



MABR



304

A cold (–78 °C) solution of MABR (0.18 M, 1.7 mL, 0.31 mmol) in DCM was prepared according to the procedure described by Yamamoto and coworkers.[140] The above mentioned solution was added to a cold (–78 °C) solution of oxirane **302** (66 mg, 0.16 mmol) in DCM (3 mL). The resulting reaction mixture was allowed to stir for 30 min. TLC analysis of the mixture indicated that the starting material had been consumed. 10% aq. HCl (5 mL) and DCM (5 mL) were added and the layers were separated. The organic layer was washed with sat. aq $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (5 g of silica gel, 9:1 petroleum ether-Et_2O) to provide ketone **304** (61 mg, 92%) as a clear oil which exhibited:

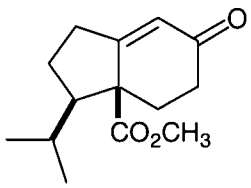
IR (film): ν = 2952, 1724, 1722, 1255, 1091, 836 cm^{-1}.

^1H NMR (400 MHz): δ = −0.01 (s, 3 H, Si-C$\underline{H}_3$), 0.00 (s, 3 H, Si-C$\underline{H}_3$),), 0.79 (d, 3 H, J = 6.2 Hz, Me-16 or Me-17), 0.84 (s, 9 H, Si-C(C$\underline{H}_3$)$_3$), 0.95 (d, 3 H, J = 6.2 Hz, Me-16 or Me-17), 1.05-1.15 (ddd, 1 H, J = 13.1, 13.1, 3.8 Hz, H-2α), 1.20-1.52 (m, 7 H), 1.63-1.94 (m, 5 H), 2.07 (s, 3 H, Me-11), 2.24-2.34 (ddd, 1 H, J = 12.6, 11.0, 4.3 Hz, H-4), 2.63-2.71 (ddd, 1 H, J = 13.1, 3.4, 3.4 Hz, H-2β), 3.48-3.62 (m, 2 H, H-14), 3.63 (s, 3 H, Me-1').

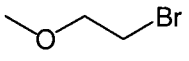
^{13}C NMR (100 MHz): δ = −5.4 (2 C, −ve, Si-$\underline{C}H_3$), 18.3 (+ve, Si-$\underline{C}(CH_3)_3$), 22.3 (−ve, C-16 or C-17), 22.6 (−ve, C-16 or C-17), 25.5 (+ve), 25.9 (3 C, −ve, Si-C($\underline{C}H_3)_3$), 27.8 (+ve), 28.2 (−ve), 28.4 (+ve), 31.8 (−ve), 35.4 (+ve), 35.9 (−ve), 36.0 (+ve), 50.8 (−ve), 54.5 (−ve), 57.2 (+ve, C-1), 57.4 (−ve), 57.9 (−ve), 60.8 (+ve, C-14), 174.4 (+ve, C-10), 212.5 (C-11).

Exact mass calculated for $C_{24}H_{44}O_4Si$: 424.3009; found: 424.3007.

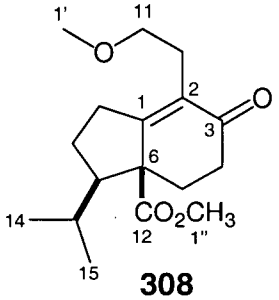
Methyl (6*S,7*R**)-7-isopropyl-2-(2-methoxyethyl)-3-oxobicyclo[4.3.0]non-1-ene-6-carboxylate (308)**



197



319



308

To a stirred suspension of NaH (2.821 g of a 60% suspension in mineral oil, 70.5 mmol) in dry DME (115 mL) at r.t. was added a solution of enone **197** (15.14 g, 64.1 mmol) in dry DME (50 mL) and the resulting mixture was allowed to stir for 1 h. During this time the reaction mixture became dark purple in colour. Neat 2-bromoethyl methyl ether (**319**, 9.08 mL, 13.43 g, 96.6 mmol) was added via a syringe. The resulting mixture was allowed to stir at r.t. for 2 days. Sat. aq NH_4Cl (100 mL) was added and the resulting mixture was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (700 g of silica gel, 3:1 petroleum ether-Et_2O) to afford enone **308** (12.84 g, 68%) as a clear oil.

IR (film): ν = 2952, 1725, 1665, 1356, 1230, 1170, 1112 cm^{-1}.

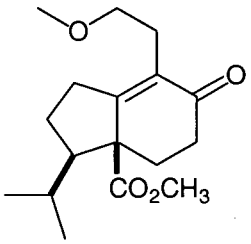
^1H NMR (400 MHz): δ = 0.84 (d, 3 H, J = 6.5 Hz, Me-14 or Me-15), 1.00 (d, 3 H, J = 6.5 Hz, Me-14 or Me-15), 1.41-1.75 (m, 4 H), 1.93-2.02 (m, 1 H), 2.28-2.36 (ddd, 1 H, J = 18.2, 5.2, 2.4 Hz), 2.35-2.42 (dd, 1 H, J = 13.4-4.7 Hz), 2.41-2.48 (br. dd, 2 H, J = 7, 7 Hz), 2.50-2.62 (ddd, 1 H, J = 17.6, 8.9, 8.9 Hz), 2.68-2.79 (dd, 1 H, J = 19.9, 10.1 Hz), 2.78-2.85 (ddd, 1 H, J = 13.0, 4.7, 2.5 Hz), 3.24 (s, 3 H, Me-1'), 3.25-3.32 (m, 2 H, H-11), 3.64 (s, 3 H, Me-1").

^{13}C NMR (100 MHz): δ = 22.0 (−ve, C-14 or C-15), 22.4, (−ve, C-14 or C-15), 26.8 (+ve), 27.7 (+ve), 29.6 (+ve), 30.6 (−ve), 33.5 (+ve), 34.7 (+ve), 51.8 (−ve), 57.1 (+ve, C-6), 58.4 (−ve), 58.5 (−ve), 70.8 (+ve, C-11), 129.9 (+ve, C-2), 167.9 (+ve, C-1), 172.0 (+ve, C-12), 197.8 (+ve, C-3).

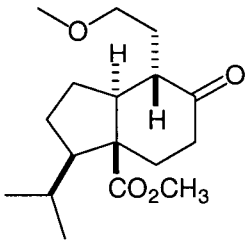
Exact mass calculated for $C_{17}H_{26}O_4$: 294.1831; found: 294.1831.

Methyl (1*S,5*S**,6*S**,9*R**)-9-isopropyl-5-(2-methoxyethyl)-4-oxobicyclo[4.3.0] nonane-1-carboxylate (309) and**

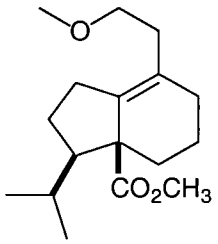
Methyl (6*S,7*R**)-7-isopropyl-2-(2-methoxyethyl)bicyclo[4.3.0]non-1-ene-6-carboxylate (321)**



308



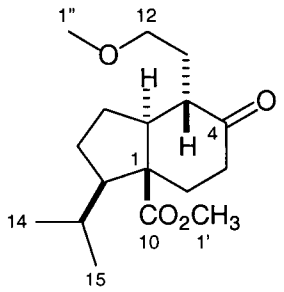
309



321

To a solution of enone **308** (12.84 g, 43.6 mmol) in MeOH (200 mL) at r.t. was added palladium-on-carbon (10%, 1 g, 0.94 mmol). The resulting heterogeneous mixture was purged with H_2 (g) three times. The mixture was allowed to stir overnight at r.t. under H_2 (g) at one atmosphere. TLC analysis of the mixture indicated that the starting material had been consumed. The mixture was filtered through a pad of Celite® (10 g) and the Celite® was rinsed with MeOH (50 mL). The collected eluate was transferred to a 500 mL round-bottomed flask and concentrated HCl (~10M, 5 mL) was added. The solution was allowed to stir overnight. H_2O (200 mL) and Et_2O (200 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (200 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and concentrated. The residual material was purified by flash column chromatography (700 g of silica gel, 7:3 petroleum ether-Et_2O) to afford ketone **309** (10.08 g, 78%) and alkene **321** (2.08 g, 17%) as clear oils.

Ketone **309** exhibited:



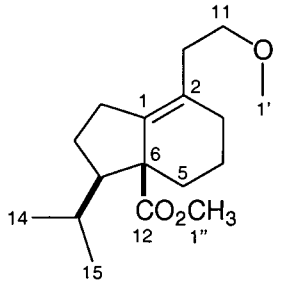
IR (film): ν = 2945, 1724, 1712, 1458, 1215, 1117 cm^{-1}.

^1H NMR (400 MHz): δ = 0.83 (d, 3 H, = 6.2 Hz, Me-14 or Me-15), 0.96 (d, 3 H, J = 6.2 Hz, Me-14 or Me-15), 1.32-1.47 (m, 2 H), 1.47-1.52 (ddd, 1 H, J = 12.9, 12.9, 5.5 Hz), 1.56-1.77 (m, 3 H), 1.79-2.07 (m, 4 H), 2.29-2.38 (ddd, 1 H, J = 15.6, 5.5, 2.5 Hz), 2.39-2.53 (m, 2 H), 2.74-2.83 (ddd, 1 H, J = 13.0, 6.7, 2.2 Hz, H-2β), 3.24 (s, 3 H, Me-1"), 3.30-3.38 (ddd, 1 H, J = 14.4, 7.5, 7.2 Hz, H-12), 3.39-3.46 (ddd, 1 H, J = 9.4, 7.5, 5.2 Hz, H-12), 3.72 (s, 3 H, Me-1').

^{13}C NMR (100 MHz): δ = 22.2 (−ve, C-14 or C-15), 22.6 (−ve, C-14 or C-15), 25.7 (+ve), 27.2 (+ve), 29.9 (+ve), 31.8 (−ve), 34.8 (+ve), 39.2 (+ve), 48.7 (−ve), 51.3 (−ve), 55.3 (−ve), 57.0 (+ve, C-1), 57.4 (−ve), 58.4 (−ve), 70.8 (+ve, C-12), 174.1 (+ve, C-10), 211.8 (+ve, C-4).

Exact mass calculated for $C_{17}H_{28}O_4$: 296.1988; found: 296.1987

Alkene **321** exhibited:



IR (film): ν = 2951, 1723, 1459, 1365, 1164, 1117 cm^{-1}.

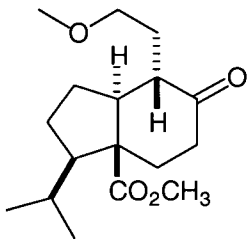
^1H NMR (400 MHz): δ = 0.85 (d, 3 H, *J* = 6.5 Hz, Me-14 or Me-15), 0.95-1.04 (m, 1 H), 1.01 (d, 3 H, *J* = 6.5 Hz, Me-14 or Me-15), 1.25-1.35 (ddd, 1 H, *J* = 11.9, 7.4, 7.4 Hz), 1.35-1.57 (m, 3 H), 1.68-1.76 (m, 1 H), 1.79-1.97 (m, 3 H), 2.17-2.37 (m, 3 H), 2.41-2.52 (m, 1 H), 2.64-2.71 (ddd, 1 H, *J* = 12.6, 3.4, 3.4 Hz, H-5β), 3.30 (s, 3 H, Me-1'), 3.33-3.38 (m, 2 H, H-11), 3.60 (s, 3 H, Me-1").

^{13}C NMR (100 MHz): δ = 20.7 (+ve), 22.2 (−ve, C-14 or C-15), 22.7 (−ve, C-14 or C-15), 27.3 (+ve), 27.4 (+ve), 28.5 (+ve), 30.9 (−ve), 33.0 (+ve), 34.1 (+ve), 51.1 (−ve), 56.0 (+ve, C-6), 58.5 (−ve), 58.7 (−ve), 71.0 (+ve, C-11), 126.7 (+ve, C-2), 139.0 (+ve, C-1), 175.2 (+ve, C-12).

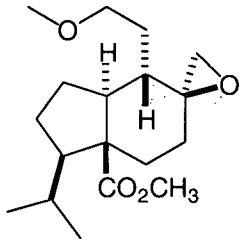
Exact mass calculated for $C_{17}H_{28}O_3$: 280.2038; found: 280.2034.

Methyl (1*S, 4*R**, 5*S**, 6*S**, 9*R**)-4-formyl-9-isopropyl-5-(2-methoxyethyl)bicyclo [4.3.0]nonane-1-carboxylate (310)** and

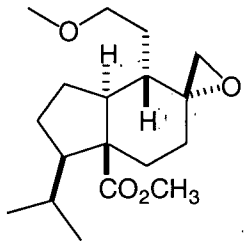
Methyl (1*S, 4*S**, 5*S**, 6*S**, 9*R**)-4-formyl-9-isopropyl-5-(2-methoxyethyl)bicyclo [4.3.0]nonane-1-carboxylate (327)**



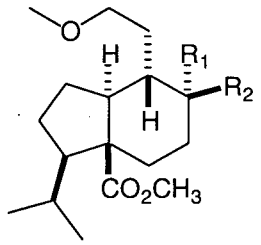
309



325



326



310: R_1 = H, R_2 = CHO
327: R_1 = CHO, R_2 = H

To a cold (0 °C) solution of $Me_3S^+I^-$ (885 mg, 4.33 mmol) in THF (20 mL) was added dry KHMDS (865 mg, 4.33 mmol) in portions over 30 min. The resulting reaction mixture was stirred for 1 h. A solution of ketone **309** (988 mg, 3.33 mmol) in THF (15 mL) was transferred to the reaction vessel via a cannula. The reaction mixture was stirred for 30 min. H_2O (10 mL) was added and the mixture was concentrated. The residue was partitioned between Et_2O (20 mL) and H_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (20 mL). The combined organic extracts were washed with H_2O (10 mL), brine (20 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified using flash column chromatography (50 g of silica gel, 7:3 petroleum ether-Et_2O) to afford an inseparable mixture of epoxides **325** and **326**.

The acquired mixture of epoxides **325** and **326** was dissolved in DCM (10 mL) and the resulting solution was cooled to –78 °C. A cold (–78 °C) solution of MABR[140] (22 mL of a 0.18 M solution in DCM, 3.67 mmol) was transferred to the reaction vessel via a cannula. The resulting mixture was stirred for 1 h. 10% aq HCl (20 mL) and DCM (10 mL) were added and the layers were separated. The organic layer was washed with sat. aq $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated. The residual oil was purified by flash column chromatography (50 g of silica gel, 7:3 petroleum ether-Et_2O)

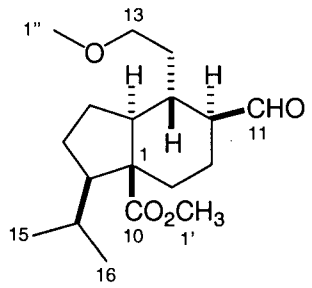
to yield an inseparable mixture of aldehydes **310** and **327** (ratio 3:1, 0.981 g, 95%) as a clear oil.

The mixture of aldehydes **310** and **327** exhibited:

IR (film): ν = 2951, 2872, 1720, 1705, 1456, 1169 cm^{-1}.

Exact mass calculated for $C_{18}H_{30}O_4$: 310.2144; found: 310.2143.

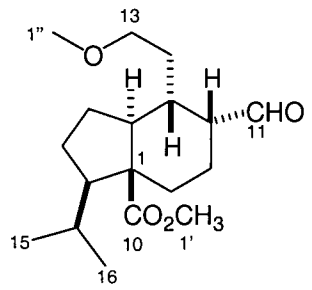
Aldehyde **310** exhibited



^{1}H NMR (400 MHz): δ = 0.79 (d, 3 H, J = 6.5 Hz, Me-15 or Me-16), 0.95 (d, 3 H, J = 6.4 Hz, Me-15 or Me-16), 1.10-1.95 (series of m, 12 H), 1.99-2.07 (m, 1 H), 2.51-2.57 (ddd, 1 H, J = 13.3, 3.3, 3.3 Hz), 2.53-2.63 (m, 1 H), 3.27 (s, 3 H, Me-1"), 3.38-3.49 (m, 2 H), 3.64 (s, 3 H, Me-1'), 9.85 (s, 1 H, H-11).

^{13}C NMR (100 MHz): δ = 22.3 (−ve, C-15 or C-16), 22.7 (−ve, C-15 or C-16), 24.1 (+ve), 25.3 (+ve), 28.3 (+ve), 30.2 (+ve), 31.8 (−ve), 33.4 (+ve), 37.1 (−ve), 48.4 (−ve), 50.8 (−ve), 52.3 (−ve), 57.6 (+ve, C-1), 58.1 (−ve), 58.6 (−ve), 71.1 (+ve, C-13), 174.5 (+ve, C-10), 205.6 (−ve, C-11).

Compound **327** exhibited:

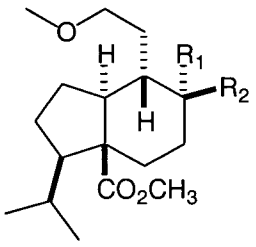


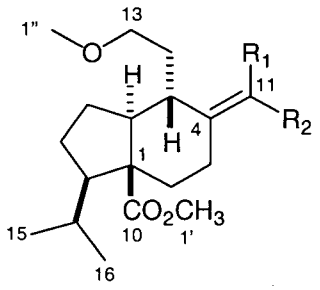
^{1}H NMR (400 MHz): δ = 0.81 (d, 3 H, J = 6.9 Hz, Me-15 or Me-16), 0.98 (d, 3 H, J = 6.3 Hz, Me-15 or Me-16), 1.10-1.95 (series of m, 13 H), 2.06-2.16 (m, 1 H), 2.68-2.75 (ddd, 1 H, J = 12.9, 3.3, 3.3 Hz), 3.22 (s, 3 H, Me-1"), 3.25-3.38 (m, 2 H, H-13), 3.66 (s, 3 H, Me-1'), 9.47 (d, 1 H, J = 3.9 Hz, H-11).

^{13}C NMR (100 MHz): δ = 22.3 (−ve, C-15 or C-16), 22.7 (−ve, C-15 or C-16), 24.7 (+ve), 25.3 (+ve), 28.3 (+ve), 31.8 (−ve), 32.2 (+ve), 34.8 (−ve), 35.3 (+ve), 50.9 (−ve), 54.1 (−ve), 55.2 (−ve), 57.0 (+ve, C-1), 58.0 (−ve), 58.4 (−ve), 69.9 (+ve, C-13), 174.3 (+ve, C-10), 204.5 (−ve, C-11).

Methyl (1*S,4*E*,5*S**,6*S**,9*R**)-9-isopropyl-5-(2-methoxyethyl)-4-*tert*-butyldimethylsiloxymethylenebicyclo[4.3.0]nonane-1-carboxylate (342)** and

Methyl (1*S,4*Z*,5*S**,6*S**,9*R**)-9-isopropyl-5-(2-methoxyethyl)-4-*tert*-butyldimethylsiloxymethylenebicyclo[4.3.0]nonane-1-carboxylate (343)**





310: R_1 = H, R_2 = CHO
327: R_1 = CHO, R_2 = H

342: R_1 = H, R_2 = OTBS
343: R_1 = OTBS, R_2 = H

To a cold (–78 °C), stirred solution of KHMDS (1.93 g, 9.68 mmol) in THF (20 mL) was added a cold (–78 °C) solution of aldehydes **310** and **327** (2.00 g, 6.45 mmol) in THF (10 mL). The resulting mixture was allowed to warm to 0 °C over 1 h. A cold (0 °C) solution of TBSCl (1.46 g, 9.68 mmol) in THF (20 mL) was transferred to the reaction vessel via a cannula. The resulting mixture was allowed to warm to r.t. overnight. H_2O (50 mL) and Et_2O (50 mL) were added and the layers were separated. The aqueous layer was washed with Et_2O (50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (100 g of silica gel, 9:1 petroleum ether-Et_2O) to yield silyl enol ethers **342** and **343** (2.06 g, 75%).

Although the two silyl enol ethers (ratio 0.8:1) could be separated and characterized independently, no effort was made to establish the geometry about the double bond of the major product.

The major isomer exhibited:

IR (film): ν = 2954, 2860, 1724, 1666, 1462, 1255, 1161, 839 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.07 (s, 6 H, Si-C$\underline{H}_3$), 0.78 (d, 3 H, J = 6.4 Hz, Me-15 or Me-16), 0.88 (s, 9 H, Si-C(C$\underline{H}_3$)$_3$), 0.95 (d, 3 H, J = 6.3 Hz, Me-15 or Me-16), 1.08-1.17 (ddd, 1 H, J = 13.0, 10.3, 7.0 Hz), 1.16-1.64 (m, 5 H), 1.65-1.98 (m, 5 H), 2.05-2.13 (m, 1 H), 2.49-2.59 (ddd, 1 H, J = 10.3, 6.3, 4.3 Hz), 2.61-2.70 (ddd, 1 H, J = 12.6, 6.2, 4.0 Hz), 3.28 (s, 3 H, Me-1''), 3.30-3.40 (m, 2 H, H-13), 3.60 (s, 3 H, Me-1'), 6.00 (s, 1 H, H-11).

^{13}C NMR (100 MHz): δ = −5.3 (2 C, −ve, Si-$\underline{C}$H$_3$), 18.2 (+ve, Si-$\underline{C}$(CH$_3$)$_3$), 21.4 (+ve), 22.3 (−ve, C-15 or C-16), 22.6 (−ve, C-15 or C-16), 25.7 (3 C, −ve, Si-C($\underline{C}$H$_3$)$_3$), 25.9 (+ve), 29.1 (+ve), 30.4 (+ve), 31.7 (−ve), 35.7 (+ve), 38.3 (−ve), 50.7 (−ve), 55.9 (−ve), 57.5 (+ve, C-1), 58.1 (−ve), 58.5 (−ve), 71.1 (+ve, C-13), 121.6 (+ve, C-4), 132.7 (−ve, C-11), 174.9 (+ve, C-10).

Exact mass calculated for $C_{24}H_{44}O_4Si$: 424.3008; found: 424.3009.

The minor isomer exhibited:

^{1}H NMR (400 MHz): δ = 0.08 (s, 6 H, Si-C$\underline{H}_3$), 0.79 (d, 3 H, J = 6.5 Hz, Me-15 or Me-16), 0.90 (s, 9 H, Si-C(C$\underline{H}_3$)$_3$), 0.91 (d, 3 H, J = 6.5 Hz, Me-15 or Me-16), 1.11-1.32 (m, 2 H), 1.32-1.46 (m, 2 H), 1.46-1.60 (m, 2 H), 1.64-1.98 (m, 5 H), 2.04-2.17 (m, 1 H), 2.62-2.72 (m, 1 H), 2.67-2.76 (ddd, 1 H, J = 13.1, 10.0, 7.7 Hz), 3.28 (s, 3 H, Me-1''), 3.29-3.43 (m, 2 H, H-13), 3.57 (s, 3 H, Me-16), 5.97 (s, 1 H, H-11).

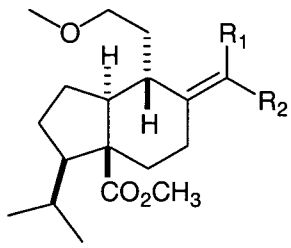
^{13}C NMR (100 MHz): δ = −5.2 (−ve, Si-$\underline{C}$H$_3$), −5.1 (−ve, Si-$\underline{C}$H$_3$), 18.0 (+ve, Si-$\underline{C}$(CH$_3$)$_3$), 22.1 (−ve, C-15 or C-16), 22.6 (−ve, C-15 or C-16), 22.9 (+ve), 25.6 (3 C, −ve, Si-C($\underline{C}$H$_3$)$_3$), 27.1 (+ve), 30.2 (+ve), 31.8 (−ve), 33.6 (+ve), 35.2 (+ve), 36.2 (−ve), 50.7 (−ve), 52.5 (−ve), 56.2 (+ve, C-1), 58.5 (−ve), 58.9 (−ve), 72.4 (+ve, C-13), 119.2 (+ve, C-4), 134.0 (−ve, C-11), 175.3 (+ve, C-10).

No IR or mass spectral data were collected on this material.

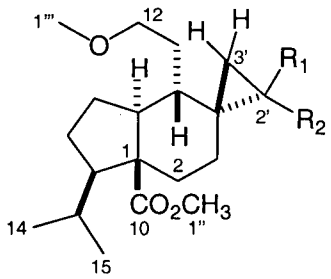
Methyl (1*S,2'*R**,4*S**,5*S**,6*S**,9*R**)-9-isopropyl-5-(2-methoxyethyl)-2'-*tert*-butyl dimethylsiloxybicyclo[4.3.0]nonane-4-spiro-1'cyclopropane-1-carboxylate (344)**

and

Methyl (1*S,2'*S**,4*S**,5*S**,6*S**,9*R**)-9-isopropyl-5-(2-methoxyethyl)-2'-*tert*-butyl dimethylsiloxybicyclo[4.3.0]nonane-4-spiro-1'cyclopropane-1-carboxylate (345)**



342: R_1 = H, R_2 = OTBS
343: R_1 = OTBS, R_2 = H



344: R_1 = H, R_2 = OTBS
345: R_1 = OTBS, R_2 = H

To a solution of silyl enol ethers **342** and **343** (2.737 g, 6.45 mmol) and diethylzinc (16.1 mL of a 1.0 M solution in hexanes, 16.1 mmol) in Et_2O (25 mL) at r.t. was added, drop-wise, via a syringe, diiodomethane (6.91 g, 2.08 mL, 25.8 mmol). The resulting reaction mixture was allowed to stir for 4 h. Et_2O (100 mL) and 1 M aq HCl (25 mL) were added and the layers were separated. The organic layer was washed successively with sat. aq $NaHCO_3$ (25 mL) and brine (25 mL). The organic extracts were dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (125 g of silica gel, 9:1 petroleum ether-Et_2O) to afford an inseparable mixture of spirocyclopropyl silyl ethers **344** and **345** (ratio 0.8:1, 1.634 g, 60%) as a clear oil. A mixture of silyl enol ethers **342** and **343** (245 mg, 9%) was also recovered from the reaction mixture.

A clean sample of the major spirocyclopropyl silyl enol ether was synthesized from the major silyl enol ether following the procedure described above. This material exhibited:

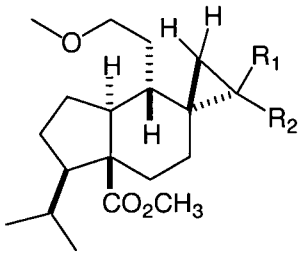
IR (film): ν = 2953, 2860, 1725, 1462, 1197, 1157, 1120, 838 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.02 (s, 3 H, Si-C$\underline{H}_3$), 0.04 (s, 3 H, Si-C$\underline{H}_3$), 0.11-0.15 (dd, 1 H, J = 6.2, 3.4 Hz, H-3'), 0.63-0.80 (dd, 1 H, J = 6.7, 6.2 Hz, H-3'), 0.80 (d, 3 H, J = 6.5 Hz, Me-14 or Me-15), 0.84 (s, 9 H, Si-C(C$\underline{H}_3$)$_3$), 0.98-1.08 (m, 1 H), 0.99 (d, 3 H, J = 6.5 Hz, Me-14 or Me-15), 1.10-1.48 (m, 5 H), 1.48-1.78 (m, 5 H), 1.80-2.00 (m 2 H), 2.48-2.56 (ddd, 1 H, J = 12.7, 3.6, 3.6 Hz, H-2β), 3.13-3.21 (ddd, 1 H, J = 9.3, 9.3, 6.5 Hz, H-12), 3.21-3.25 (dd, 1 H, J = 6.7, 3.4 Hz, H-2'), 3.26 (s, 3 H, Me-1'''), 3.32-3.40 (ddd, 1 H, J = 9.3, 9.3, 5.4 Hz, H-14), 3.64 (s, 3 H, Me-1'').

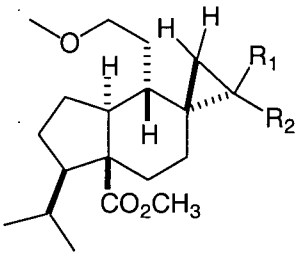
^{13}C NMR (100 MHz): δ = −5.0 (−ve, Si-$\underline{C}$H$_3$), −4.9 (−ve, Si-$\underline{C}$H$_3$), 17.8 (+ve, Si-$\underline{C}$(CH$_3$)$_3$, 22.4 (−ve, C-14 or C-15), 22.6 (−ve, C-14 or C-15), 25.6 (+ve), 25.7 (−ve), 25.8 (−ve, 3 C, Si-C($\underline{C}$H$_3$)$_3$), 26.0 (+ve), 28.4 (+ve), 28.6 (+ve), 28.6 (+ve), 31.9 (−ve), 35.6 (+ve), 37.9 (−ve), 50.6 (−ve), 52.7 (−ve), 56.4 (−ve), 57.9 (−ve), 58.0 (+ve, C-1), 58.5 (−ve), 72.8 (+ve, C-12), 175.1 (+ve, C-10).

Exact mass calculated for $C_{25}H_{46}O_4Si$: 438.3165; found: 438.3168.

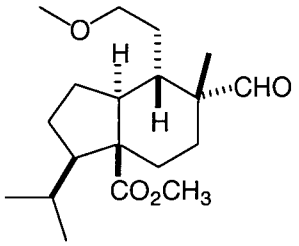
Methyl (1*S,4*S**,5*S**,6*S**,9*R**)-4-formyl-9-isopropyl-5-(2-methoxyethyl)-4-methylbicyclo[4.3.0]nonane-1-carboxylate (311)**



344: R_1 = H, R_2 = OTBS
345: R_1 = OTBS, R_2 = H



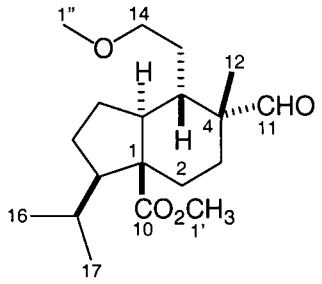
346: R_1 = H, R_2 = OH
347: R_1 = OH, R_2 = H



311

To a solution of spirocyclopropyl silyl ethers **344** and **345** (1.63 g, 3.73 mmol) in THF (25 mL) was added a solution of TBAF (5 mL of a 1.0 M solution in THF, 5 mmol) and the resulting reaction mixture was stirred for 7 h. H_2O (25 mL) and Et_2O (25 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (25 mL). The combined organic extracts were washed with brine (25 mL) and concentrated to furnish a crude mixture of spirocyclopropanols **346** and **347**.

The acquired crude mixture of spirocyclopropanols **346** and **347** was dissolved in THF (20 mL) and concentrated aq HCl (~10 M, 1 mL) was added. The resulting reaction mixture was heated to 70 °C for 1 h. Et_2O (25 mL) and H_2O (25 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (100 g of silica gel, 7:3 petroleum ether-Et_2O) to provide aldehyde **311** (665 mg, 55% over two steps) as a colourless oil.



311

Aldehyde **311** exhibited:

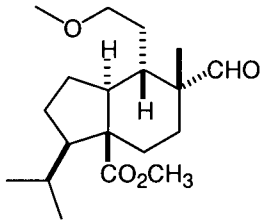
IR (film): ν = 2950, 2873, 1721, 1460, 1365, 1194, 1118 cm^{-1}.

^1H NMR (400 MHz): δ = 0.78 (d, 3 H, J = 6.4 Hz, Me-16 or Me-17), 0.94 (d, 3 H, J = 6.3 Hz, Me-16 or Me-17), 1.04 (s, 3 H, Me-12), 1.14-1.46 (m, 6 H), 1.61-1.74 (m, 2 H), 1.77-1.98 (m, 5 H), 2.44-2.52 (ddd, 1 H, J = 12.9, 3.2, 3.2 Hz, H-2β), 3.22-3.31 (m, 1 H, H-14), 3.28 (s, 3 H, Me-1"), 3.37-3.45 (ddd, 1 H, J = 9.1, 9.1, 5.1 Hz, H-14), 3.64 (s, 3 H, Me-1'), 9.58 (s, 1 H, H-11).

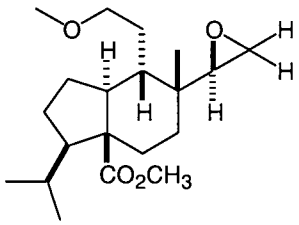
^{13}C NMR (100 MHz): δ = 22.2 (−ve), 22.3 (−ve), 22.6 (−ve), 25.7 (+ve), 28.4 (+ve), 29.5 (+ve), 31.8 (−ve), 33.5 (+ve), 33.7 (+ve), 42.1 (−ve), 49.9 (+ve, C-4), 50.7 (−ve), 53.3 (−ve), 57.6 (−ve), 57.7 (+ve, C-1), 58.5 (−ve), 73.0 (+ve, C-14), 174.5 (+ve, C-10), 206.7 (−ve, C-11).

Exact mass calculated for $C_{19}H_{32}O_4$: 324.2301; found: 324.2300.

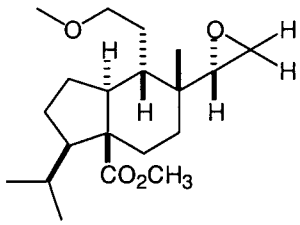
Methyl (1*S,4*S**,5*S**,6*S**,9*R**)-4-formylmethyl-9-isopropyl-5-(2-methoxyethyl)-4-methylbicyclo[4.3.0]nonane-1-carboxylate (318)**



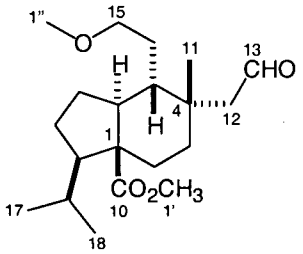
311



348



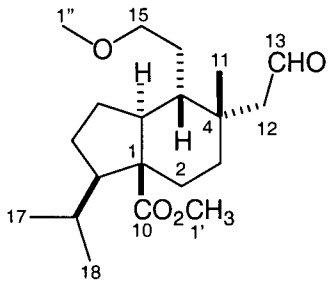
349



318

To a cold (0 °C) solution of $Me_3S^+I^-$ (1.05 g, 5.12 mmol) in THF (40 mL) was added dry KHMDS (1.02 g, 5.12 mmol) in portions over 30 min. The resulting reaction mixture was stirred for 1 h. A solution of aldehyde **311** (1.11 g, 3.42 mmol) in THF (15 mL) was transferred to the reaction vessel via a cannula. The reaction mixture was stirred for 30 min. H_2O (10 mL) was added and the mixture was concentrated. The residue was partitioned between Et_2O (20 mL) and H_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (20 mL). The combined organic extracts were washed with H_2O (10 mL), brine (20 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified using flash column chromatography (50 g of silica gel, 7:3 petroleum ether-Et_2O) to afford an inseparable mixture of epoxides **348** and **349**.

The acquired mixture of epoxides **348** and **349** was dissolved in DCM (10 mL) and the resulting solution was cooled to –78 °C. A cold (–78 °C) solution of MABR[140] (27 mL of a 0.15 M solution in DCM, 4.1 mmol) was transferred to the reaction vessel via a cannula. The resulting mixture was stirred for 1 h. 10% aq HCl (20 mL) and DCM (10 mL) were added and the layers were separated. The organic layer was washed with sat. aq $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated. The residual oil was purified by flash column chromatography (50 g of silica gel, 7:3 petroleum ether-Et_2O) to yield aldehyde **318** (0.923 g, 89% over two steps) as a clear oil.



318

Aldehyde **318** exhibited:

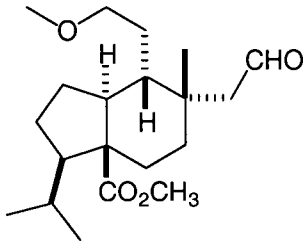
IR (film): ν = 2951, 1720, 1457, 1364, 1192 cm^{-1}.

^1H NMR (400 MHz): δ = 0.80 (d, 3 H, J = 6.5 Hz, Me-17 or Me-18), 0.98 (d, 3 H, J = 6.4 Hz, Me-17 or Me-18), 1.10 (s, 3 H, Me-11), 1.19-1.45 (m, 7 H), 1.56-1.72 (m, 4 H), 1.82-2.03 (m, 2 H), 2.14-2.21 (dd, 1 H, J = 14.0, 1.2 Hz), 2.42-2.52 (m, 2 H), 3.23-3.32 (m, 1 H, H-15), 3.30 (s, 3 H, Me-1"), 3.41-3.49 (ddd, 1 H, J = 9.3, 9.3, 4.6 Hz, H-15), 3.65 (s, 3 H, Me-1'), 9.81 (dd, 1 H, J = 3.9, 2.7 Hz, H-13).

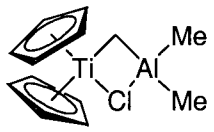
^{13}C NMR (100 MHz): δ = 22.3 (−ve, C-17 or C-18), 22.7 (−ve, C-17 or C-18), 25.5 (+ve), 27.0 (−ve), 28.4 (+ve), 29.6 (+ve), 31.8 (−ve), 32.4 (+ve), 36.4 (+ve), 37.5 (+ve, C-4), 45.0 (−ve), 45.4 (+ve, C-12), 50.8 (−ve), 51.4 (−ve), 57.6 (−ve), 57.9 (+ve, C-1), 58.6 (−ve, C-1'), 73.0 (+ve, C-15), 174.6 (+ve, C-10), 204.0 (−ve, C-13).

Exact mass calculated for $C_{20}H_{34}O_4$: 338.2457; found: 338.2460.

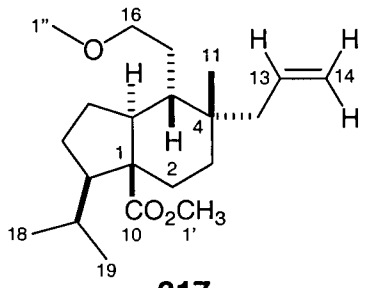
Methyl (1*S,4*S**,5*S**,6*S**,9*R**)-4-allyl-9-isopropyl-5-(2-methoxyethyl)-4-methyl bicyclo[4.3.0]nonane-1-carboxylate (317)**



318



146



317

To a cold (0 °C) solution of aldehyde **318** (88 mg, 0.26 mmol) in THF (2 mL) was added Tebbe's reagent (**146**, 573 μL of a 0.5 M solution in toluene, 0.29 mmol). The resulting reaction mixture was allowed to warm up to r.t. over 1 h. The reaction mixture was diluted with Et_2O (5 mL) and aq NaOH (500 μL of a 0.1 M solution) was added in a dropwise fashion via a syringe. H_2O (5 mL) was added and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (5 g of silica gel, 19:1 petroleum ether-Et_2O) to afford alkene **317** (70 mg, 80%) as a clear oil which exhibited:

IR (film): ν = 2951, 2877, 1722, 1637, 1458, 1191, 1157, 1119 cm^{-1}.

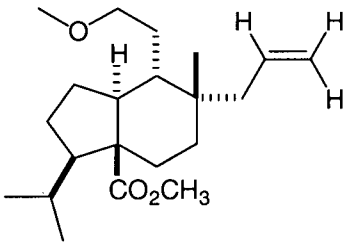
^1H NMR (400 MHz): δ = 0.79 (d, 3 H, J = 6.6 Hz, Me-18 or Me-19), 0.82 (s, 3 H, Me-11), 0.95-1.05 (m, 1 H), 0.98 (d, 3 H, J = 6.4 Hz, Me-18 or Me-19), 1.14-1.42 (m, 6 H), 1.49-1.56 (ddd, 1 H, J = 14.4, 3.1, 3.1 Hz), 1.56-1.77 (m, 3 H), 1.77-1.85 (m, 1 H), 1.86-1.99 (m, 2 H), 2.15-2.25 (dd, 1 H, J = 13.6, 8.1 Hz), 2.33-2.41 (ddd, 1 H, J = 13.1, 3.4, 3.4 Hz, H-2β), 3.21-3.29 (ddd, 1 H, J = 9.1, 9.1, 6.6 Hz, H-16), 3.29 (s, 3 H, Me-1"), 3.41-3.49 (ddd, 1 H, J = 10.5, 9.1, 5.0 Hz, H-16), 3.63 (s, 3 H, Me-1'), 4.92-5.02 (m, 2 H, H-14), 5.66-5.79 (dddd, 1 H, J = 17.0, 10.2, 8.0, 6.9 Hz, H-13).

^{13}C NMR (100 MHz): δ = 22.3 (−ve, C-18 or C-19), 22.7 (−ve, C-18 or C-19), 25.6 (+ve), 26.5 (−ve, C-11), 28.5 (+ve), 29.3 (+ve), 31.8 (−ve), 32.4 (+ve), 34.9 (+ve), 35.4 (+ve), 36.7 (+ve, C-4), 44.6 (−ve), 50.6 (−ve), 51.2 (−ve), 57.7 (−ve), 58.1 (+ve, C-1), 58.5 (−ve), 73.6 (+ve, C-16), 116.9 (+ve, C-14), 135.5 (−ve, C-13), 174.9 (+ve, C-10).

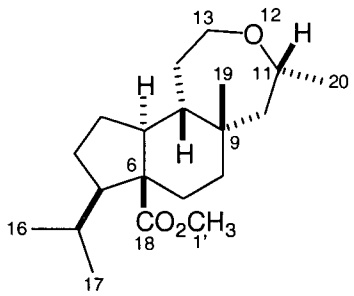
Exact mass calculated for $C_{21}H_{36}O_3$: 336.2665; found: 336.2664.

Methyl (1*S,2*S**,5*R**,6*S**,9*S**,11*R**)-5-isopropyl-9,11-dimethyl-12-oxabicyclo [7,5,0,$0^{2,6}$]tetradecane-6-carboxylate (372) and**

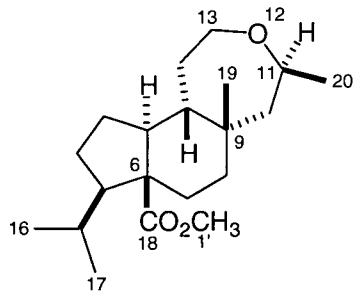
Methyl (1*S,2*S**,5*R**,6*S**,9*S**,11*S**)-5-isopropyl-9,11-dimethyl-12-oxabicyclo [7,5,0,$0^{2,6}$]tetradecane-6-carboxylate (373)**



317



372



373

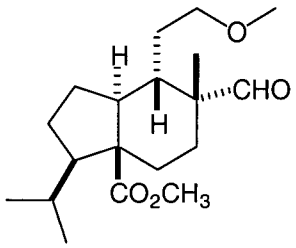
To a stirred solution of alkene **317** (20 mg, 0.059 mmol) in DCM (5 mL) was added, via a syringe, neat TMSI (100 μL, 0.70 mmol). The reaction mixture was allowed to stir for 3 h. TLC analysis of the reaction mixture mixture indicated that the starting material had been consumed. Et_2O (5 mL) was added and the reaction mixture was allowed to stir for 30 min. H_2O was added and the layers were separated. The organic layer was washed with brine (5 mL) dried ($MgSO_4$) and concentrated. The residual material was purified by flash column chromatography (1 g of silica gel, 9:1 petroleum ether-Et_2O) to yield the major tricyclic ether (**372** or **373**, 12 mg, 63%) as a clear and colourless oil.

The major isomer exhibited

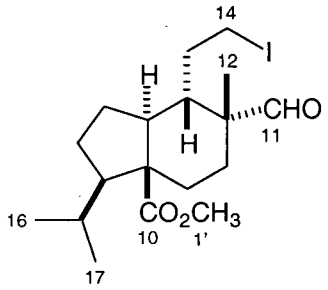
^{1}H NMR (400 MHz): δ = 0.80 (d, 3 H, J = 6.5 Hz, Me-16 or Me-17), 0.91 (s, 3 H, Me-19), 0.96-1.10 (m, 1 H), 1.00 (d, 3 H, J = 6.4 Hz, Me-16 or Me-17), 1.10-1.46 (m, 6 H), 1.48-1.74 (m, 4 H), 1.84-1.98 (m, 3 H), 1.95 (d, 3 H, J = 6.8 Hz, Me-20), 2.41-2.50 (m, 2 H), 3.44-3.48 (m, 1 H, H-13), 3.62 (s, 3 H, Me-1'), 3.63-3.68 (ddd, 1 H, J = 9.8, 9.8, 5.9 Hz, H-13), 4.20-4.26 (ddq, 1 H, J = 6.8, 6.8, 6.8 Hz, H-11).

^{13}C NMR (100 MHz): δ = 22.3 (−ve, C-16 or C-17), 22.7 (−ve, C-16 or C-17), 23.9 (−ve), 25.6 (+ve), 26.6 (−ve), 28.4 (+ve), 31.9 (−ve), 32.3 (+ve), 32.5 (−ve), 33.1 (+ve), 34.0 (+ve), 38.5 (+ve, C-9), 44.6 (+ve), 45.6 (−ve), 50.7 (−ve), 51.1 (−ve), 57.6 (−ve), 58.0 (+ve, C-6), 63.2 (+ve, C-13), 174.9 (+ve, C-18)

Methyl (1*S,4*S**,5*S**,6*S**,9*R**)-4-formyl-5-(2-iodoethyl)-9-isopropyl -4-methylbicyclo[4.3.0]nonane-1-carboxylate (375)**



311

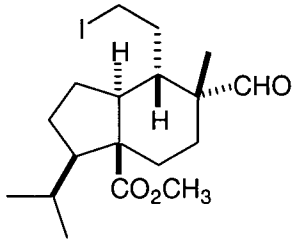


375

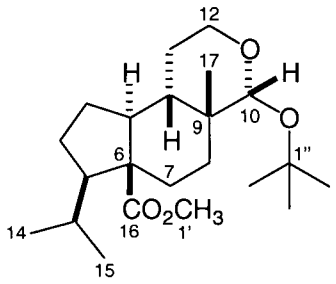
To a cold (–78 °C), stirred solution of ether 311 (3.60 g, 11.1 mmol) in DCM (100 mL) was added, via a syringe, a cold solution of TMSI (5 g, 25.0 mmol). The resulting reaction mixture was allowed to warm up to r.t. overnight. Et_2O (50 mL) was added and the reaction mixture was allowed to stir for 1 h. H_2O (50 mL) was added and the layers were separated. The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and concentrated. Attempts to purify the material by flash column chromatography on silica gel (200 g of silica gel, 9:1 petroleum ether-Et_2O) invariably resulted in the isolation of an orange oil (3.46 g, ~ 74%) which appeared clean by ^1H NMR spectroscopy. The acquired material was stored at low temperature (–5 °C) and used in the next reaction without further purification.

^1H NMR (400 MHz): δ = 0.79 (d, 3 H, J = 6.3 Hz, Me-16 or Me-17), 0.95 (d, 3 H, J = 6.4 Hz, Me-16 or Me-17), 1.08 (s, 3 H, Me-12), 1.11-1.21 (ddd, 1 H, J = 13.6, 13.6, 3.6 Hz, H-2α), 1.23-1.50 (m, 5 H), 1.64-1.75 (m, 1 H), 1.83-2.08 (m, 5 H), 2.09-2.19 (m, 1 H), 2.47-2.55 (ddd, 1 H, J = 13.6, 3.6, 3.6 Hz, H-2β), 3.06-3.15 (ddd, 1 H, J = 8.6, 8.6, 8.6 Hz, H-14), 3.29-3.37 (ddd, 1 H, J = 8.6, 8.6, 4.9 Hz, H-14), 3.68 (s, 3 H, Me-1'), 9.48 (s, 1 H, H-11).

Methyl (1*S,2*S**,5*R**,6*S**,9*R**)-5-isopropyl-9-methyl-10-*tert*-butoxy-11-oxabicyclo [7.4.0.0^{2,6}]tridecane-6-carboxylate (385)**



375



385

To a stirred solution of iodide **375** (43 mg, 0.10 mmol) in THF (5 mL) at r.t was added *t*-BuOK (17 mg, 0.15 mmol) in one portion. The resulting heterogeneous reaction mixture was allowed to stir for 30 min. H_2O (5 mL) and Et_2O (5 mL) were added and the phases were separated. The organic phase was washed with brine (5 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (4 g of silica gel, 93:7 petroleum ether-Et_2O) to furnish mixed acetal **385** (32 mg, 87%) as a clear oil which exhibited:

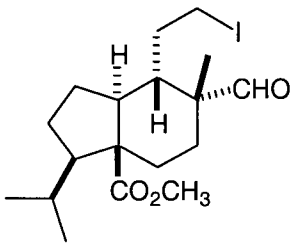
IR (film): ν = 2972, 1721, 1508, 1364, 1165, 1088 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.82 (d, 3 H, *J* = 6.5 Hz, Me-14 or Me-15), 0.94 (s, 3 H, Me-17), 0.94-1.06 (m, 1 H), 1.00 (d, 3 H, *J* = 6.4 Hz, Me-14 or Me-15), 1.07-1.34 (m, 3 H), 1.19 (s, 9 H, O-C(C$\underline{H}_3$)$_3$), 1.39-1.50 (m, 2 H), 1.54-1.82 (m, 4 H), 1.87-1.96 (m, 1 H), 1.94-2.05 (m, 1 H), 2.12-2.23 (ddd, 1 H, *J* = 12.2, 12.2, 9.0 Hz), 2.38-2.45 (ddd, 1 H, *J* = 13.0, 3.6, 3.6 Hz, H-7β), 3.52-3.65 (m, 1 H, H-12), 3.65 (s, 3 H, Me-1'), 3.70-3.77 (m, 1 H, H-12), 4.80 (s, 1 H, H-10).

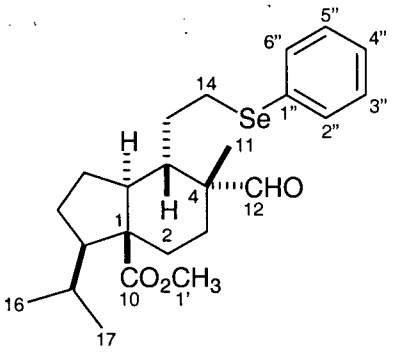
^{13}C NMR (100 MHz): δ = 21.3 (−ve), 22.3 (−ve), 22.7 (−ve), 24.1 (+ve), 25.6 (+ve), 28.7 (+ve), 28.8 (3 C, −ve, O-C($\underline{C}$H$_3$)$_3$), 31.9, (−ve), 32.8 (+ve), 33.4 (+ve), 37.1 (+ve, C-9), 42.2 (−ve), 47.9 (−ve), 50.7 (−ve), 57.6 (+ve, C-6), 58.5 (−ve, C-1'), 61.7 (+ve, C-12), 74.3 (+ve, O-$\underline{C}$(CH$_3$)$_3$), 94.9 (−ve, C-10), 174.8 (+ve, C-16).

Exact mass calculated for $C_{22}H_{38}O_4$: 366.2770; found: 366.2769.

Methyl (1*S,4*R**,5*S**,6*S**,9*R**)-4-formyl-9-isopropyl-4-methyl-5-(2-phenylselanyl-ethyl)bicyclo[4.3.0]nonane-1-carboxylate (378)**



375



378

To a stirred solution of diphenyl diselenide (1.54 g, 4.93 mmol) in EtOH (25 mL) at r.t. was added $NaBH_4$ (373 mg, 9.87 mmol) in three portions over 10 minutes. The reaction mixture was stirred until the yellow solution became colourless. A solution of iodide **375** (3.456 g, 8.23 mmol) in EtOH (10 mL) was transferred to the reaction vessel via a cannula and the reaction mixture was heated to reflux for 2 h. H_2O (30 mL) and Et_2O (30 mL) were added and the layers were separated. The aqueous layer was washed with Et_2O (30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (175 g of silica gel, 9:1 petroleum ether-Et_2O) to furnish aldehyde **378** (3.46 g, 94%) as a clear oil which exhibited:

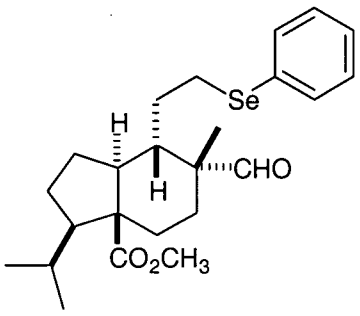
IR (film): ν = 2948, 1720, 1476, 1364, 1148 cm^{-1}.

^1H NMR (400 MHz): δ = 0.78 (d, 3 H, J = 6.2 Hz, Me-16 or Me-17), 0.95 (d, 3 H, J = 6.2 Hz, Me-16 or Me-17), 0.97 (s, 3 H, Me-11), 1.13-1.22 (ddd, 1 H, J = 13.4, 13.4, 3.4 Hz), 1.22-1.46 (m, 4 H), 1.47-1.55 (m, 1 H), 1.55-1.67 (m, 1 H), 1.76-2.02 (m, 6 H), 2.45-2.53 (ddd, 1 H, J = 13.1, 3.2, 3.2 Hz, H-2β), 2.75-2.85 (ddd, 1 H, J = 11.9, 9.8, 7.2 Hz, H-14), 3.03-3.12 (ddd, 1 H, J = 11.9, 10.2, 5.1 Hz, H-14), 3.66 (s, 3 H, Me-1'), 7.18-7.26 (m, 3 H), 7.42-7.48 (m, 2 H), 9.51 (s, 1 H, H-12).

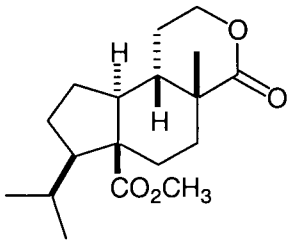
^{13}C NMR (100 MHz): δ = 22.2 (−ve), 22.3 (−ve), 22.6 (−ve), 25.8 (+ve), 28.5 (+ve), 28.6 (+ve), 30.3 (+ve), 31.8 (−ve), 33.6 (+ve), 33.6 (+ve), 46.3 (−ve), 50.2 (+ve, C-4), 50.8 (−ve), 53.2 (−ve), 57.5 (−ve), 57.7 (+ve, C-1), 126.8 (−ve, C-1"), 129.0 (2 C, −ve, C-2" and C-6"), 130.1 (+ve, C-1'), 132.6 (2 C, −ve, C-3" and C-5"), 174.5 (+ve, C-10), 206.4 (−ve, C-12).

Exact mass calculated for $C_{24}H_{34}O_3{}^{80}Se$: 450.1673; found: 450.1673.

Methyl (1S*,2S*,5R*,6S*,9R*)-5-isopropyl-9-methyl-10-oxo-11-oxatricyclo[7.4.0.02'6]tridecane-6-carboxylate (390)



378



390

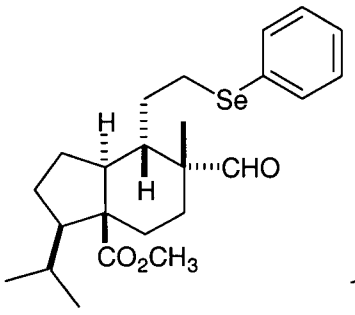
A stream of O_2 and O_3 was passed thorugh a cold (–78 °C), stirred solution of selenide **378** (55 mg, 0.12 mmol) in DCM (5 mL) until a grey-blue colour persisted. Benzene (5 mL) was added and the resulting solution was heated to reflux for 1 h. The resulting solution was allowed to cool to r.t. Et_2O (10 mL) and H_2O (10%, 10 mL) were added and the layers were separated. The organic layer was washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (5 g of silica gel, 19:1 petroleum ether-Et_2O) to provide lactone **390** (27 mg, 72%) as a clear and colourless oil.

IR (film): ν = 2952, 1724, 1448, 1166, 1013 cm^{-1}.

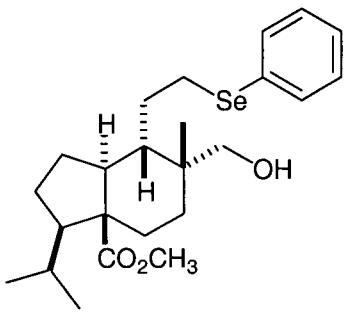
^1H NMR (400 MHz): δ = 0.80 (d, 3 H, J = 6.5 Hz), 0.99 (d, 3 H, J = 6.4 Hz), 1.12-1.33 (m, 3 H), 1.26 (s, 3 H), 1.35-1.50 (m, 2 H), 1.54-1.71 (m, 3 H), 1.79-2.01 (m, 3 H), 2.26-2.39 (m, 1 H), 2.39-2.56 (m, 2 H), 3.66 (s, 3 H), 4.32-4.43 (m, 2 H).

^{13}C NMR (100 MHz): δ = 21.7 (+ve), 22.2 (−ve), 22.6 (−ve), 24.7 (+ve), 27.1 (−ve), 28.6 (+ve), 31.7 (−ve), 34.2 (+ve), 34.9 (+ve), 40.2 (−ve), 44.4 (+ve), 50.9 (−ve), 51.0 (−ve), 57.2 (+ve), 58.1 (−ve), 66.9 (+ve), 174.5 (+ve), 176.2 (+ve).

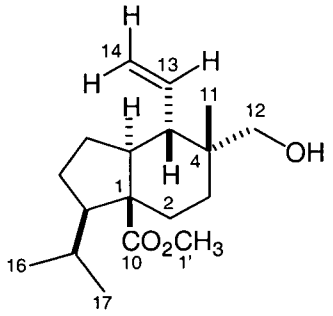
Methyl (1*S,4*R**,5*S**,6*S**,9*R**)-4-hydroxymethyl-9-isopropyl-4-methyl-5-vinyl bicyclo[4.3.0]nonane-1-carboxylate (393)**



378



392



393

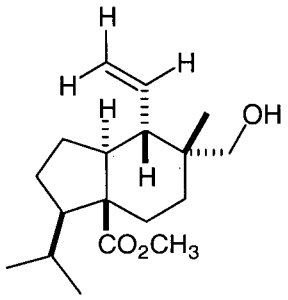
To a stirred solution of aldehyde **378** (3.46 g, 7.69 mmol) in MeOH (20 mL) at r.t. was added $NaBH_4$ (238 mg, 11.6 mmol). The reaction mixture was allowed to stir for 1 h. The reaction mixture was diluted with Et_2O (20 mL) and was transferred to a separatory funnel. 10% aq HCl (20 mL) was added and the layers were separated. The aqueous layer was washed with Et_2O (20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (200 g of silica gel, 6:4 petroleum ether-Et_2O) to afford alcohol **393** (3.26 g, 93%) as a clear oil.

A stream of O_2 and O_3 was passed thorugh a cold (–78 °C), stirred solution of alcohol **392** (3.26 g, 7.22 mmol) in DCM (25 mL) until a grey-blue colour persisted. Benzene (25 mL) and triethylamine (5 mL) were added and the resulting solution was heated to reflux for 1 h. The resulting solution was allowed to cool to r.t. Diethyl ether (25 mL) and aq. HCL (10%, 25 mL) were added. The layers were separated and the organic layer was washed successively with sat. aq. $NaHCO_3$ (25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography to provide alcohol **393** (1.68 g, 79% yield) as a clear and colourless oil.

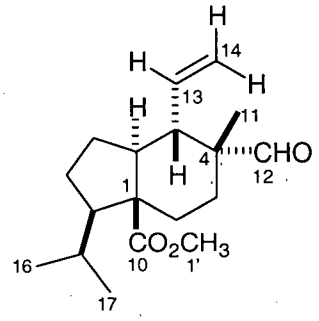
H NMR (400 MHz): δ = 0.80 (d, 3 H, J = 6.5 Hz, Me-16 or Me-17), 0.86 (s, 3 H, Me-11), 1.00 (d, 3 H, J = 6.4 Hz, Me-17), 1.06-1.16 (ddd, 1 H, J = 14.1, 14.1, 3.5 Hz, H-2α), 1.20-1.34 (m, 3 H), 1.34-1.50 (m, 3 H), 1.64-1.75 (m, 1 H), 1.76-1.83 (ddd, 1 H, J = 14.7, 3.4, 3.4 Hz), 1.83-1.91 (m, 1 H), 2.01-2.09 (dd, 1 H, J = 12.1, 10.0 Hz), 2.42-2.50 (ddd, 1 H, J = 14.1, 3.4, 3.4 Hz, H-2β), 3.49 (d, 1 H, J = 10.8 Hz, H-12), 3.66 (s, 3 H, H-1'), 3.68 (d, 1 H, J = 10.8 Hz, H-12), 4.97-5.00 (m, 1 H, H-14), 5.00-5.05 (m, 1 H, H-14), 5.42-5.56 (ddd, 1 H, J = 17.0, 10.0, 10.0 Hz, H-13). The hydroxyl proton was not observed in this spectrum.

^{13}C NMR (100 MHz): δ = 22.3 (−ve, C-16 or C-17), 22.7 (−ve, C-16 or C-17), 25.0 (−ve, C-11), 25.8 (+ve), 28.6 (+ve), 31.9 (−ve), 32.9 (+ve), 33.2 (+ve), 38.3 (+ve, C-4), 49.5 (−ve), 50.7 (−ve), 52.8 (−ve), 57.6 (+ve, C-1), 58.1 (−ve), 65.5 (+ve, C-12), 116.7 (+ve, C-14), 137.4 (−ve, C-13), 174.7 (+ve, C-10).

Methyl (1*S,4*R**,5*S**,6*S**,9*R**)-4-formyl-9-isopropyl-4-methyl-5-vinylbicyclo[4.3.0] nonane-1-carboxylate (377)**



393



377

Alcohol **393** was oxidized to aldehyde **377** using the method developed by Ley.[88] Thus, to a stirred solution of alcohol **377** (1.68g , 5.7 mmol) in DCM (25 mL) at r.t. was added, sequentially, TPAP (200 mg, 0.57 mmol) in one portion and NMO (995 mg, 8.5 mmol) in one portion. The mixture was allowed to stir overnight. The reaction mixture was filtered through a pad of silica gel (10 g) and the silica gel was rinsed with Et_2O. The collected eluate was concentrated and the residual oil was purified by flash column chromatography (100 g of silica gel, 19:1 petroleum ether-Et_2O) to yield aldehyde **377** (1.31 g, 4.5 mmol, 78%) as a clear oil which exhibited.

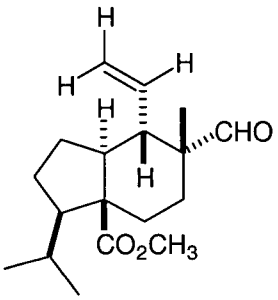
IR (film): ν = 2953, 1720, 1638, 1459, 1365, 1167 cm^{-1}.

^1H NMR (400 MHz): δ = 0.79 (d, 3 H, J = 6.5 Hz, Me-16 or Me-17), 0.96 (d, 3 H, J = 6.4 Hz, Me-16 or Me-17), 0.99 (s, 3 H, Me-11), 1.21-1.44 (m, 5 H), 1.44-1.55 (m, 1 H), 1.64-1.77 (m, 1 H), 1.80-1.98 (m, 3 H), 2.05-2.15 (dd, 1 H, J = 11.6, 11.6 Hz), 2.47-2.56 (m, 1 H), 3.66 (s, 3 H, Me-1'), 5.05-5.12 (m, 2 H, H-14), 5.72-5.84 (m, 1 H, H-13), 9.56 (s, 1 H, H-12).

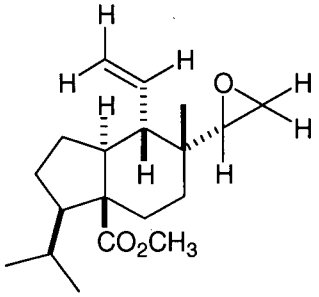
^{13}C NMR (100 MHz): δ = 22.2 (−ve), 22.3 (−ve), 22.7 (−ve), 25.7 (+ve), 28.6 (+ve), 31.8 (−ve), 32.7 (+ve), 33.5 (+ve), 49.5 (+ve, C-4), 50.8 (−ve), 50.9 (−ve), 52.2 (−ve), 57.2 (+ve, C-1), 58.0 (−ve), 118.0 (+ve, C-14), 136 (−ve, C-13), 174.5 (+ve, C-10), 206.5 (−ve , C-12).

Exact mass calculated for $C_{18}H_{28}O_3$: 292.2038; found: 292.2038.

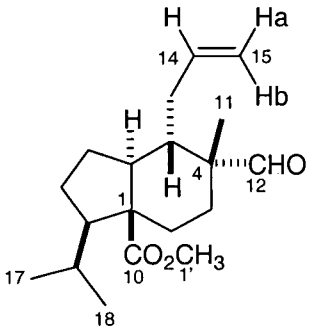
Methyl (1*S,4*R**,5*S**,6*S**,9*R**)-5-allyl-4-formyl-9-isopropyl-4-methylbicyclo[4.3.0] nonane-1-carboxylate (398)**



377



394



398

To a cold (0 °C) solution of $Me_3S^+I^-$ (1.37 g, 6.72 mmol) in THF (50 mL) was added dry KHMDS (1.34 g, 6.72 mmol) in portions over 30 min. The resulting reaction mixture was stirred for 1 h. A solution of aldehyde **377** (1.31 g, 4.46 mmol) in THF (20 mL) was transferred to the reaction vessel via a cannula. The reaction mixture was stirred for 30 min. H_2O (10 mL) was added and the mixture was concentrated. The residue was partitioned between Et_2O (25 mL) and H_2O (25 mL). The layers were separated and the aqueous layer was extracted with Et_2O (25 mL). The combined organic extracts were washed with H_2O (15 mL), brine (25 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified using flash column chromatography (70 g of silica gel, 9:1 petroleum ether-Et_2O) to afford an inseparable mixture of epoxides **394** (1.34 g, 98%).

The acquired mixture of epoxides **394** was dissolved in DCM (10 mL) and the resulting solution was cooled to –78 °C. A cold (–78 °C) solution of MABR[140] (53 mL of a 0.10 M solution in DCM, 5.3 mmol) was transferred to the reaction vessel via a cannula. The resulting mixture was allowed to warm up to r.t. overnight. 10% aq HCl (30 mL) and DCM (20 mL) were added and the layers were separated. The organic layer was washed with sat. aq $NaHCO_3$ (30 mL), dried ($MgSO_4$), and concentrated. The residual oil was purified by flash column chromatography (70 g of silica gel, 9:1 petroleum ether-Et_2O) to yield aldehyde **398** (636 mg, 47%) as a clear oil.

Aldehyde **398** exhibited:

IR (film): ν = 2952, 2873, 1719, 1459, 1366, 1165, 910 cm^{-1}.

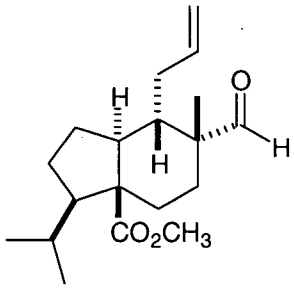
^1H NMR (400 MHz): δ = 0.80 (d, 3 H, J = 6.4 Hz, Me-17 or Me-18), 0.96 (d, 3 H, J = 6.4 Hz, Me-17 or Me-18), 1.08 (s, 3 H, Me-11), 1.21-1.44 (m, 6 H), 1.59-1.73 (m, 2 H), 1.81-1.97 (m, 4 H), 2.21-2.31 (m, 1 H), 2.34-2.43 (dddd, 1 H, J = 15.2, 8.1, 3.7, 1.7 Hz), 2.45-2.56 (m, 1 H), 3.66 (s, 3 H, Me-1'), 4.91-4.96 (ddd, 1 H, J = 10.1, 3, 1.5 Hz, H-15a), 4.96-5.02 (ddd, 1 H, J = 17.0, 3.0, 1.7 Hz, H-15b), 5.74-5.87 (dddd, 1 H, J = 17.0, 10.1, 7.0, 7.0 Hz, H-14).

^{13}C NMR (100 MHz): δ = 22.3 (−ve), 22.6 (−ve), 22.7 (−ve), 25.9 (+ve), 28.6 (+ve), 31.8 (−ve), 33.6 (+ve), 33.8 (+ve), 34.1 (+ve), 46.0 (−ve), 49.9 (+ve, C-4), 50.8 (−ve), 52.9 (−ve), 57.7 (−ve), 57.9 (+ve, C-1), 115.4 (+ve, C15), 139.1 (−ve, C-14), 174.6 (+ve, C-10), 207.0 (−ve, C-12).

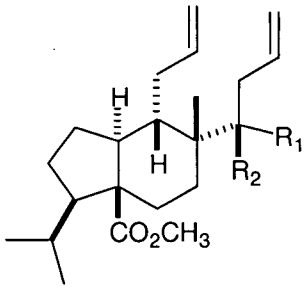
Exact mass calculated for $C_{19}H_{30}O_3$: 306.2195; found: 306.2194.

Methyl (1*S,2*S**,5*R**,6*S**,9*R**,10*R**)-10-hydroxy-5-isopropyl-9-methyltricyclo [7.5.0.0^{2,6}]tetradec-12-ene-6-carboxylate (416)** and

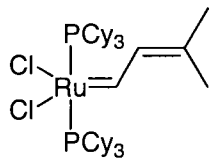
Methyl (1*S,2*S**,5*R**,6*S**,9*R**,10*S**)-10-hydroxy-5-isopropyl-9-methyltricyclo [7.5.0.0^{2,6}]tetradec-12-ene-6-carboxylate (417)**



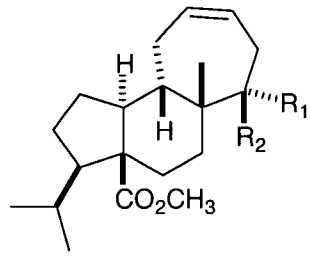
398



414: R_1 = H, R_2 = OH
415: R_1 = OH, R_2 = H



403



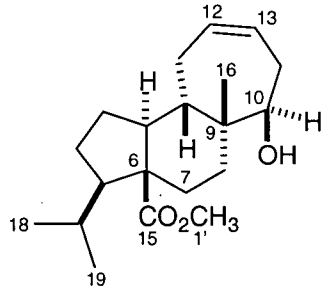
416: R_1 = H, R_2 = OH
417: R_1 = OH, R_2 = H

To a cold (0 °C), stirred solution of aldehyde **398** (636 mg, 2.07 mmol) in THF (25 mL) was added, via a syringe, allyl magnesium bromide (2.1 mL of a 1.0 M solution in diethyl ether, 2.1 mmol). After 10 min, TLC analysis of the mixture indicated that all the starting material had been consumed. Sat. aq. NH_4Cl (15 mL) was added and the layers were separated. The organic layer was washed with brine (15 mL), dried ($MgSO_4$) and concentrated. The residual oil was purified by flash column chromatography (30 g of silica gel, 3:1 petroleum ether-Et_2O) to furnish a nearly 1:1 mixture of alcohols **414** and **415** (687 mg, 95%) as a clear oil.

To a solution of alcohols **414** and **415** (111 mg, 0.32 mmol) in degassed DCM was added, via a cannula, a solution of catalyst **403** (36 mg, 0.044 mmol) in degassed DCM. The resulting solution was heated to reflux for 24 h. The reaction mixture was allowed to cool to r.t. and filtered through a pad of silica gel (2 g). The silica gel was rinsed with Et_2O. The combined eluate was concentrated and the residual oil was purified by flash column chromatography (7 g of silica gel, 7:3 petroleum ether, Et_2O) silica to provide a nearly 1:1 mixture of tricyclic alcohols **416** and **417** (90 mg, 88%) as a clear oil.

Clean samples of alcohols **416** and **417** were obtained by flash column chromatography (silica gel, 7:3 petroleum ether-Et_2O).

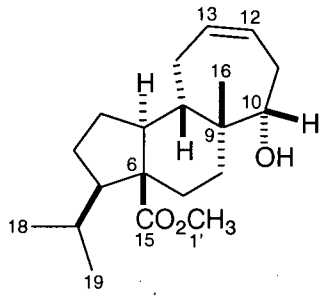
Compound **416** exhibited



^{1}H NMR (400 MHz): δ = 0.79 (d, 3 H, J = 6.5 Hz, Me-18 or Me-19), 0.99 (d, 3 H, J = 6.3 Hz, Me-18 or Me-19), 0.98 (s, 3 H, Me-16), 1.00-1.10 (ddd, 1 H, J = 14.6, 13.3, 3.7 Hz, H-7α), 1.10-1.20 (m, 1 H), 1.20-1.31 (m, 1 H), 1.31-1.49 (m, 4 H), 1.51-1.60 (m, 1 H), 1.79-1.98 (m, 4 H), 1.98-2.05 (ddd, 1 H, J = 4.6, 3.2, 3.2 Hz), 2.02-2.10 (m, 1 H), 2.39-2.46 (ddd, 1 H, J = 13.3, 3.4, 3.4 Hz, H-7β), 2.44-2.52 (m, 1 H), 2.55-2.65 (m, 1 H), 3.65 (s, 3 H, Me-1'), 3.84-3.92 (br. d, 1 H, J = 11.4 Hz, H-10), 5.62-5.76 (m, 2 H, H-12 and H-13).

^{13}C NMR (100 MHz): δ = 20.5 (−ve, C-16), 22.3 (−ve, C-18 or C-19), 22.7 (−ve, C-18 or C-19), 24.7 (+ve), 25.5 (+ve), 28.7 (+ve), 31.9 (−ve), 32.1 (+ve), 33.2 (+ve), 35.9 (+ve), 42.4 (+ve, C-9), 44.9 (−ve), 48.0 (−ve), 50.8 (−ve), 58.1 (−ve), 58.4 (+ve, C-6), 67.7 (−ve, C-10), 127.7 (−ve, C-12 or C-13), 131.2 (−ve, C-12 or C-13), 175.3 (+ve, C-15).

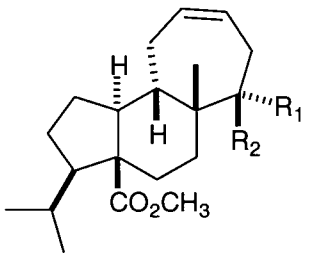
Compound **417** exhibited



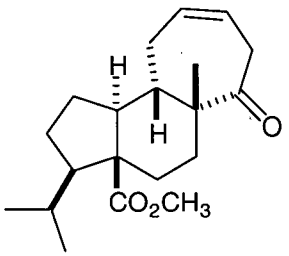
^{1}H NMR (400 MHz): δ = 0.78 (d, 3 H, J = 6.5 Hz, Me-18 or Me-19), 0.90 (s, 3 H, Me-16), 0.96 (d, 3 H, J = 6.4 Hz, Me-18 or Me-19), 1.17-1.31 (m, 1 H), 1.32-1.48 (m, 4 H), 1.48-1.59 (m, 2 H), 1.70-1.93 (m, 4 H), 2.03-2.13 (m, 2 H), 2.28-2.38 (ddd, 1 H, J = 14.6, 7.1, 7.1 Hz), 2.42-2.59 (m, 3 H), 3.46-3.53 (dd, 1 H, J = 7.0, 7.0 Hz, H-10), 3.63 (s, 3 H, Me-1'), 5.63-5.71 (m, 1 H, H-12 or H-13), 5.82-5.91 (m, 1 H, H-12 or H-13).

^{13}C NMR (100 MHz): δ = 22.2 (−ve, C-18 or C-19), 22.7 (−ve, C-18 or C-19), 25.5 (+ve), 26.3 (+ve), 28.7 (+ve), 29.4 (−ve), 31.9 (−ve), 32.5 (+ve), 35.8 (+ve), 38.7 (+ve), 41.1 (+ve, C-9), 43.1 (−ve), 49.4 (−ve), 50.5 (−ve), 57.6 (+ve, C-6), 58.4 (−ve), 78.7 (−ve, C-10), 127.7 (−ve, C-12 or C-13), 132.7 (−ve, C-12 or C-13), 175.4 (+ve, C-15).

Methyl (1*S,2*S**,5*R**,6*S**,9*R**)-5-isopropyl-9-methyl-10-oxotricyclo[7.5.0.0^{2,6}] tetradec-12-ene-6-carboxylate (402)**



416: R_1 = H, R_2 = OH
417: R_1 = OH, R_2 = H



402

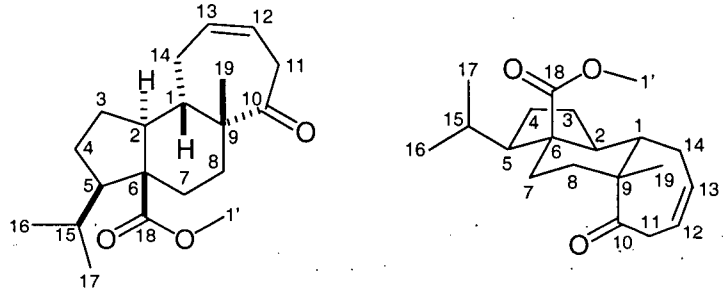
A mixture of alcohols **416** and **417** was oxidized to ketone **402** using the method developed by Ley.[88] Thus, to a stirred solution of alcohols **416** and **417** (50 mg, 0.16 mmol) in DCM (5 mL) at r.t. was added, sequentially, TPAP (5 mg, 0.015 mmol) in one portion and NMO (35 mg, 0.30 mmol) in one portion. The mixture was allowed to stir overnight. The reaction mixture was filtered through a pad of silica gel (1 g) and the silica gel was rinsed with Et_2O. The collected eluate was concentrated and the residual oil was purified by flash column chromatography (5 g of silica gel, 17:3 petroleum ether-Et_2O) to yield ketone **402** (45 mg, 90%) as a clear oil which exhibited.

IR (film): ν = 2951, 1720, 1698, 1365, 1155, 679 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.77 (d, 3 H, J = 6.5 Hz), 0.92-1.02 (ddd, 1 H, J = 14.3, 13.8, 4.1 Hz), 0.96 (d, 3 H, J = 6.4 Hz), 1.19-1.29 (m, 1 H), 1.27 (s, 3 H), 1.31-1.41 (m, 2 H), 1.43-1.58 (m, 3 H), 1.76-1.94 (m, 3 H), 2.04-2.11 (ddd, 1 H, J = 14.3, 3.5, 3.3 Hz), 2.12-2.22 (ddd, 1 H, J = 14.4, 8.2, 5.6 Hz), 2.41-2.49 (ddd, 1 H, J = 13.2, 4.1, 3.5 Hz), 2.62-2.71 (dd, 1 H, J = 12.7, 8.7 Hz), 2.73-2.82 (m, 1 H), 3.64 (s, 3 H), 3.67-3.74 (m, 1 H), 5.67-3.74 (m, 1H), 5.79-5.88 (m, 1H).

^{13}C NMR (100 MHz): δ = 22.2 (−ve), 22.6 (−ve), 25.4 (+ve), 25.8 (+ve), 26.0 (−ve), 28.5 (+ve), 31.8 (−ve), 34.1 (+ve), 35.6 (+ve), 40.8 (+ve), 46.8 (−ve), 50.1 (−ve), 50.7 (−ve), 53.8 (+ve), 57.8 (+ve), 58.0 (−ve), 123.8 (−ve), 131.4 (−ve), 175.2 (+ve), 208.4 (+ve).

Table 4.20: NMR data for methyl (1*S**,2*S**,5*R**,6*S**,9*R**)-5-isopropyl-9-methyl-10-oxotricyclo[7.5.0.0^{2,6}]tetradec-12-ene-6-carboxylate (**402**)



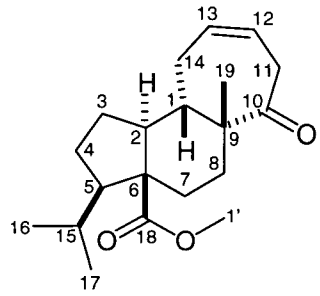
Carbon No.	^{13}C δ (ppm)[a]	^{1}H δ (ppm) (mult; *J* (Hz))[b,c,d]	HMBC Correlations[e]
1	46.8	H-1: part of the m at 1.74-1.98	H-2, H-8eq, H-14a, H-14b, H-19
2	50.1	H-2: part of the m at 1.43-1.58	H-3a, H-3b, H-7eq, H-14b
3	25.4	H-3a: part of the m at 1.43-1.58	
		H-3b: part of the m at 1.76-1.94	
4	28.5	H-4a: part of the m at 1.31-1.41	H-5, H-15
		H-4b: part of the m at 1.76-1.94	
5	58.0	H-5: part of the m at 1.31-1.41	H-16, H-17
6	57.8		H-7ax, H-8eq, H-15
7	34.1	H-7ax: part of the m at 1.43-1.58	
		H-7eq: 2.41-2.49 (ddd; 13.2, 4.1, 3.5)	
8	35.6	H-8ax: 0.92-1.02 (ddd; 14.3, 13.8, 4.1)	H-19
		H-8eq: 2.04-2.11 (ddd; 14.3, 3.5, 3.3)	
9	53.8		H-7eq, H-11a, H-14a, H-14b
10	208.4		H-1, H-8ax, H-11a, H-11b, H-19
11	40.8	H-11a: 2.62-2.71 (dd; 12.7, 8.7)	H-12, H-13
		H-11b: 3.67-3.74 (m)	
12	123.8	H-12: 5.67-5.76 (m)	H-11a, H-11b, H-14a, H-14b
13	131.4	H-13: 5.79-5.88 (m)	H-1, H-11a, H-11b, H-14a, H-14b
14	25.8	H-14a: 2.12-2.22 (ddd; 14.4, 8.2, 5.6)	H-12, H-13
		H-14b: 2.73-2.82 (m)	
15	31.8	H-15: 1.19-1.29 (m)	H-16, H-17
16	22.6	H-16: 0.77 (d; 6.4)	H-15, H-17
17	22.2	H-17: 0.96 (d; 6.5)	H-15, H-16
18	175.2		H-5, H-7ax, H-1'
19	26.0	H-19: 1.27 (s)	
1'	50.7	H-1': 3.64 (s)	

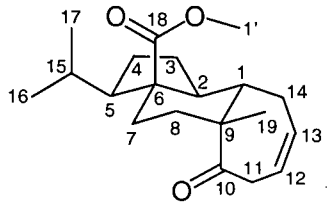
[a] Recorded at 100 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC and JMOD data.

[d] Methylene protons are designated H-Xax and H-Xeq if they are known to occupy axial and equatorial positions, respectively, in the conformation depicted above. If no information regarding their position is available then they are arbitrarily designated H-Xa and H-Xb.

[e] Only those correlations which could be unambiguously assigned are recorded.

Table 4.21: NMR data for methyl (1*S**,2*S**,5*R**,6*S**,9*R**)-5-isopropyl-9-methyl-10-oxotricyclo[7.5.0.0^{2,6}]tetradec-12-ene-6-carboxylate (**402**)





Proton No	^{1}H δ (ppm) (mult; *J* (Hz))[a,b,c]	COSY Correlations[d]
H-1	part of the m at 1.74-1.98	H-14a
H-2	part of the m at 1.43-1.58	
H-3a	part of the m at 1.43-1.58	
H-3b	part of the m at 1.76-1.94	
H-4a	part of the m at 1.31-1.41	
H-4b	part of the m at 1.76-1.94	
H-5	part of the m at 1.31-1.41	
H-7ax	part of the m at 1.43-1.58	H-7eq, H-8ax, H-8eq
H-7eq	2.41-2.49 (ddd; 13.2, 4.1, 3.5)	H-7ax, H-8ax, H-8eq
H-8ax	0.92-1.02 (ddd; 14.3, 13.8, 4.1)	H-7ax, H7eq, H-8eq
H-8eq	2.04-2.11 (ddd; 14.3, 3.5, 3.3)	H-7ax, H-7eq, H-8ax
H-11a	2.62-2.71 (dd; 12.7, 8.7)	H-11b, H-12
H-11b	3.67-3.74 (m)	H-11a, H-12, H-13
H-12	5.67-5.76 (m)	H-11a, H-11b, H-13
H-13	5.79-5.88 (m)	H-11b, H-12, H-14a, H-14b
H-14a	2.12-2.22 (ddd; 14.4, 8.2, 5.6)	H-1, H-13, H-14b
H-14b	2.73-2.82 (m)	H-13, H-14a
H-15	1.19-1.29 (m)	H-16, H-17
H-16	0.77 (d; 6.4)	H-15
H-17	0.96 (d; 6.5)	H-15
H-19	1.27 (s)	
H-1'	3.64 (s)	

[a] Recorded at 400 MHz. [b] Assignments based on HMQC and JMOD data.

[c] Methylene protons are designated H-Xax and H-Xeq if they are known to occupy axial and equatorial positions, respectively, in the conformation depicted above. If a proton occupies an α relative position it is designated H-Xα, if it occupies a β relative position it is designated H-Xβ.

[d] Only those correlations which could be unambiguously assigned are recorded.

5. References

(1) Salzberg, H. W. *From Caveman to Chemist: Circumstances and Achievements*; American Chemical Society: Washington, DC, 1990.

(2) Jaffe, B. *Crucibles: The Story of Chemistry*; Fawcett World Library: New York, 1957.

(3) A comprehensive collection of speeches and lectures can be found at the Nobel Prize Foundation website: www.nobel.se.

(4) Presentation speech, Professor H. G. Soderbaum, 1912 (see reference 3).

(5) V. Grignard, Nobel Lecture, 1912 (see reference 3).

(6) Presentation speech, Professor S. Gronowitz, 1990 (see reference 3).

(7) Nobel Prize, 1950 (see reference 3).

(8) Nobel Prize, 1979 (see reference 3).

(9) Knowles, W. S. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1998.

(10) Noyori, R. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2008.

(11) Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2024.

(12) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464.

(13) Nicolaou, K. C.; Hummel, C. W.; Pitsinos, E. N.; Nakada, M.; Smith, A. L.; Shibayama, K.; Saimoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 10082.

(14) Ternansky, R. J.; Balogh, D. W.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 4503.

(15) Fessner, W.-D.; Murty, B. A. R. C.; Worth, J.; Hunkler, D.; Fritz, H.; Prinzbach, H.; Roth, W. D.; Schleyer, P. R.; McEwen, A. B.; Maier, W. F. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 452.

(16) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320.

(17) Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greewich, CT, 1993; Vol. 2, p 27.

(18) Trost, B. M. *Science* **1991**, *254*, 1472.

(19) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3.

(20) Stinson, S. *Chem. Eng. News* **1995**, *73*, 29.

(21) Dabrah, T. T.; Kaneko, T.; Massefski, W. J.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594.

(22) Chen, C.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 10784.

(23) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424.

(24) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.

(25) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989.

(26) Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1963**, *85*, 3528.

(27) Piers, E.; Renaud, J.; Rettig, S. J. *Synthesis* **1998**, 590.

(28) Piers, E.; Walker, S. D.; Hong-Ping, Y. unpublished results.

(29) Piers, E.; McEachern, E. J. *Synlett* **1996**, 1087.

(30) Wright, A. D.; Konig, G. M.; Angerhofer, C. K.; Greenidge, P.; Linden, A.; Desqueyroux-Faundez, R. *J. Nat. Prod.* **1996**, *59*, 710.

(31) Piers, E.; Chong, J. M. *Can. J. Chem.* **1988**, *66*, 1425.

(32) Piers, E.; Karunuratne, V. *Tetrahedron* **1989**, *45*, 1089.

(33) Loyola, L. A.; Morales, G.; Rodriguez, B.; Jimenez-Barbero, J.; de la Torre, M. C.; Perales, A.; Torres, M. R. *Tetrahedron* **1990**, *46*, 5413.

(34) Piers, E.; Walker, S. D.; Armbrust, R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 635.

(35) Previous literature reports have used different structural numbering systems for kelsoene. In this thesis the kelsoane skeleton is numbered according to IUPAC protocol for tricyclic ring systems.

(36) Arnone, A.; Nasini, G.; Vajna de Pava, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2723.

(37) Konig, G. M.; Wright, A. D. *J. Org. Chem.* **1997**, *62*, 3837-3840.

(38) Schulz, S.; Messer, C.; Dettner, K. *Tetrahedron Lett.* **1997**, *38*, 2077.

(39) Nabeta, K.; Yamamoto, K.; Hashimoto, M.; Koshino, H.; Funatsuki, K.; Katoh, K. *J. Chem. Soc., Chem. Commun.* **1998**, 1485.

(40) Hashimoto, T.; Ikeda, H.; Takaoka, S.; Tanaka, M.; Asakawa, Y. *Phytochemistry* **1999**, *52*, 501.

(41) Konig, W. A.; Warmers, U. *Phytochemistry* **1999**, *52*, 1519.

(42) Warmers, U.; Wihstutz, K.; Bulow, N.; Fricke, C.; Konig, W. A. *Phytochemistry* **1998**, *49*, 1723.

(43) Nabeta, K.; Yamamoto, M.; Fukushima, K.; Katoh, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2703.

(44) Nabeta, K.; Yamamoto, M.; Koshino, H.; Fukui, H.; Fukushi, Y.; Tahara, S. *Biosci., Biotechnol., Biochem.* **1999**, *63*, 1772.

(45) Mehta, G.; Srinivas, K. *Synlett* **1999**, *5*, 555-556.

(46) Mehta, G.; Srinivas, K. *Tetrahedron Lett.* **1999**, *40*, 4877-4880.

(47) Mehta, G.; Srinivas, K. *Tetrahedron Lett.* **2001**, *42*, 2855.

(48) Fietz-Razavian, S.; Schulz, S.; Dix, I.; Jones, P. *J. Chem. Soc., Chem. Commun.* **2001**, 2154.

(49) Bach, T.; Spiegel, A. *Synlett* **2002**, 1305.

(50) Zhang, L.; Koreeda, M. *Org. Lett.* **2002**, *4*, 3755.

(51) Fukui, H.; Fukushi, Y.; Tahara, S. *Tetrahedron Lett.* **1999**, *40*, 325.

(52) Henry, P. M.; Davies, M.; Ferguson, G.; Philips, S.; Restivo, R. *J. Chem. Soc., Chem. Commun.* **1974**, 112.

(53) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(54) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

(55) Tietze, L. F.; Beifuss, U.; Ruther, M.; Ruhlmann, A.; Antel, J.; Sheldrick, G. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1186.

(56) Bach, T.; Spiegel, A. *Eur. J. Org. Chem.* **2002**, 645.

(57) Corey, E. J.; Guzman-Perez, A.; Loh, T. P. *J. Am. Chem. Soc.* **1994**, *116*, 3611.

(58) Cargill, R. L.; Dalton, J. R.; Morton, G. H.; Caldwell, W. E. *Org. Synth.* **1984**, *1984*, 118.

(59) Meyers, A. I.; Fleming, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 306.

(60) Ramaiah, M. *Synthesis* **1984**, 529.

(61) Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467.

(62) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, 671.

(63) Franck-Neumann, M.; Kastler, A. *Synlett* **1995**, 61.

(64) Lipshutz, B. H.; Sengupta, S. *Organic Reactions* **1992**, *41*, 135.

(65) Suggs, J. W.; Cox, S. D.; Crabtree, R. H.; Quirk, J. M. *Tetrahedron Lett.* **1981**, *22*, 303.

(66) Young, J. F.; Osborn, J. A.; Jardine, F. H.; Wilkinson, G. *Chem. Commun* **1965**, 131.

(67) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(68) Reich, H. J.; Wollowitz, S. *Organic Reactions* **1993**, *44*, 1.

(69) Dauben, W. G.; Michno, D. K. *J. Org. Chem.* **1977**, *42*, 682.

(70) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2467.

(71) Piancatelli, G.; Scettri, A.; D'Auria *Synthesis* **1982**, 245.

(72) Cheng, Y.-S.; Liu, W.-L.; Chen, S. *Synthesis* **1980**, 223.

(73) Piers, E.; Cook, K. L.; Rogers, C. *Tetrahedron Lett.* **1994**, *35*, 8573.

(74) Piers, E.; Boulet, S. L. *Synlett* **1998**, 516.

(75) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1975**, *49*, 4377.

(76) Crimmins, M. T.; Reinhold, T. L. *Organic Reactions* **1993**, *44*, 297.

(77) Majetich, G.; Defauw, J. *Tetrahedron* **1988**, *44*, 3833.

(78) Taguchi, H.; Tanaka, S.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1973**, *27*, 2465.

(79) Pine, S. H. *Organic reactions* **1993**, *43*, 1.

(80) Pine, S. H.; Shen, G. S.; Hoang, H. *Synthesis* **1991**, 165.

(81) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

(82) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417.

(83) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579.

(84) Okazoe, T.; Hibino, J.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5581.

(85) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293.

(86) Lombardo, L. *Org. Synth.* **1987**, *65*, 81.

(87) The addition of a Pb(II) source has been shown to dramatically increase the rate of olefination in the Takai and Lombardo reactions.
Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.

(88) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(89) Piers, E.; Orellana, A. *Synthesis* **2001**, *2138*.

(90) Thompson, H. W.; Weedon, B. C. L.; Cullis, C. F.; Gujral, P. D., Eds. *Nomenclature of Organic Chemistry*; Butterworth & Co.: London, 1971.

(91) Panico, R.; Powell, W. H.; Richer, J. C. *A Guide to IUPAC Nomenclature of Organic Compounds-Recommendations 1993*; Blackwell Scientific Publications: Oxford, 1993.

(92) Loyola, L. A.; Morales, G.; de la Torre, M. C.; Pedreros, S.; Rodriguez, B. *Phytochemistry* **1990**, *29*, 3950.

(93) Loyola, L. A.; Morales, G.; Rodriguez, B.; Jimenez-Barbero, J.; Pedreros, S.; de la Torre, M. C.; Perales, A. *J. Nat. Prod.* **1991**, *54*, 1404.

(94) Loyola, L. A.; Borquez, J.; Morales, G.; San Martin, A. *Phytochemistry* **1996**, *43*, 165.

(95) Nicoletti, M.; Di Fabio, A.; D'Andrea, A.; Salvatore, G.; van Baren, C.; Coussio, J. D. *Phytochemistry* **1996**, *43*, 1065.

(96) Loyola, L. A.; Borquez, J.; Morales, G.; San Martin, A. *Phytochemistry* **1997**, *44*, 649.

(97) Loyola, L. A.; Borquez, J.; Morales, G.; San Martin, A. *Phytochemistry* **1998**, *49*, 1091.

(98) Wachter, G. A.; Matooq, G.; Hoffmann, J. J.; Maiese, W. M.; Singh, M. P.; Montenegro, G.; Timmermann, B. N. *J. Nat. Prod.* **1999**, *62*, 1319.

(99) Loyola, L. A.; Borquez, J.; Morales, G.; San Martin, A. *Phytochemistry* **2000**, *53*, 961.

(100) Loyola, L. A.; Borquez, J.; Morales, G.; San Martin, A.; Manriquez, V.; Wittke, O. *Tetrahedron* **1998**, *54*, 15533.

(101) Wachter, G. A.; Franzblau, S. G.; Montenegro, G.; Suarez, E.; Fortunato, R. H.; Saavedra, E.; Timmermann, B. N. *J. Nat. Prod.* **1998**, *61*, 965.

(102) Dewick, P. M. ***Medicinal Natural Products****: A Biosynthetic Approach*; 2nd ed.; John Wiley & Sons Ltd.: Chichester, 2002.

(103) Boyd, J. D.; Foote, C. S.; Imagawa, D. K. *J. Am. Chem. Soc.* **1980**, *102*, 3641.

(104) Sutbeyaz, Y.; Secen, H.; Balci, M. *J. Org. Chem.* **1988**, *53*, 2312.

(105) Cahiez, G.; Bernard, D.; Normant, J. F. *Synthesis* **1976**, 245.

(106) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(107) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.

(108) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

(109) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Jouliie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784.

(110) Kuhnert, S. M.; Maier, M. E. *Org. Lett.* **2002**, *4*, 643.

(111) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons, Inc: New York, 1994.

(112) Lo Cicero, B.; Weisbuch, F.; Dana, G. *J. Org. Chem.* **1981**, *46*, 914.

(113) Crabtree, S. R.; Mander, L. N.; Sethi, P. *Org. Synth.* **1991**, *70*, 256.

(114) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808.

(115) Kotsuki, H.; Arimura, K.; Ohishi, T.; Maruzasa, R. *J. Org. Chem.* **1999**, *64*, 3770.

(116) Christoffers, J. *Chem. Commun* **1997**, 943.

(117) Vettel, P. R.; Coates, R. M. *J. Org. Chem.* **1980**, *45*, 5430.

(118) Scanio, C. J. V.; Hill, L. P. *Synthesis* **1970**, 651.

(119) Johnson, J. L.; Herr, M. E.; Babcock, J. C.; Fonken, A. E.; Stafford, J. E.; Heyl, F. W. *J. Am. Chem. Soc.* **1956**, *78*, 430.

(120) Caine, D. In *Comprehensive Organic Synthesis*; First ed.; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 3, pp 1-63.

(121) Walker, S. D. In *Ph. D. Thesis*; University of British Columbia: Vancouver, 2002.

(122) Challand, B. D.; Hikino, H.; Kornis, G.; Lange, G.; de Mayo, P. *J. Org. Chem.* **1969**, *34*, 794.

(123) Baldwin, S. W.; Wilkinson, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 3634.

(124) Bader, A. R.; Carroll, M. F. *J. Am. Chem. Soc.* **1953**, *75*, 5400.

(125) Thompson, H. W. *J. Org. Chem.* **1971**, *36*, 2577.

(126) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(127) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(128) Hughes, D. L. *Organic Reactions* **1992**, *42*, 335.

(129) Corey, E. J.; Engler, T. A. *Tetrahedron Lett.* **1984**, *25*, 149.

(130) Stork, G.; Kahne, D. H. *J. Am. Chem. Soc.* **1983**, *105*, 1072.

(131) Evans, D. A.; Morrisey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.

(132) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348.

(133) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841.

(134) This protocol can also be used to prepare allenes from propargilic alcohols. Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

(135) A different protocol for this transformation has been reported by Tsuji. Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *Tetrahedron* **1993**, *49*, 5483.

(136) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

(137) NBSH can also be used to effect the deoxygenation of unhindered alcohols Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572.

(138) Barrero, A. F.; Oltra, J. E.; Alvarez, M.; Rosales, A. *J. Org. Chem.* **2002**, *67*, 5461.

(139) McKenzie, T. C. *J. Org. Chem.* **1974**, *39*, 629.

(140) Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983.

(141) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379.

(142) Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1417.

(143) Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 4039.

(144) Molander, G. A.; Quirmbach, M. S.; Silva, L. F.; Spencer, K. C.; Balsells, J. *Org. Lett.* **2001**, *3*, 2257.

(145) Miaskiewicz, K.; Smith, D. A. *J. Am. Chem. Soc.* **1998**, *120*, 1872.

(146) Bach, R. D.; Dmitrenko, O.; Waldemar, A.; Schambony, S. *J. Am. Chem. Soc.* **2003**, *125*, 924.

(147) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875.

(148) Grieco, P. A.; Noguez, J. A.; Masaki, Y. *J. Org. Chem.* **1977**, *42*, 495.

(149) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773.

(150) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

(151) Harada, K.; Munegumi, T. In *Comprehensive Organic Synthesis*; First ed.; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 8, pp 139-158.

(152) McCombie, S. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 8, pp 811-833.

(153) Corey, E. J.; Chaykovski, M. *J. Am. Chem. Soc.* **1962**, *84*, 866.

(154) Corey, E. J.; Chaykovski, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782.

(155) Corey, E. J.; Chaykovski, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(156) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843.

(157) Ireland, R. E.; Mander, L. N. *J. Org. Chem.* **1967**, *32*, 689.

(158) Malhotra, S. K.; Johnson, F. *J. Am. Chem. Soc.* **1965**, *87*, 5493.

(159) Snider, B. B.; Vo, N. H.; O'neil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644.

(160) DePuy, C. H.; Breitbeil, F. W. *J. Am. Chem. Soc.* **1963**, *85*, 2176.

(161) DePuy, C. H.; Gibson, D. H. *Chem. Rev.* **1974**, *74*, 605.

(162) Wenkert, E.; Berges, D. A. *J. Am. Chem. Soc.* **1967**, *89*, 2508.

(163) Wenkert, E.; Mueller, R. A.; Reardon, E. J.; Sathe, S. S.; Scharf, D. J.; Tosi, G. *J. Am. Chem. Soc.* **1970**, *92*, 7428.

(164) Reusch, W.; Grimm, K.; Karoglan, J. E.; Martin, J.; Subrahamanian, K. P.; Venkataramani, P. S.; Yordy, J. D. *J. Am. Chem. Soc.* **1977**, 1958.

(165) Reusch, W.; Yordy, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 1965.

(166) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323.

(167) Charette, A. B.; Beauchemin, A. *Organic reactions* **2001**, *58*, 1.

(168) Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 8000.

(169) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1483.

(170) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947.

(171) Bieber, L. W.; de Sa, A. C. P. F.; Menezes, P. H.; Goncalves, S. M. C. *Tetrahedron Lett.* **2001**, *42*, 4597.

(172) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697.

(173) Armstrong, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.

(174) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(175) Furstner, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3012.

(176) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

(177) Wilhelm, T. E.; Belderrain, T. R.; Brown, S. N.; Grubbs, R. H. *Organometallics* **1997**, *16*, 3867.

(178) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.

(179) Horst Friebolin's book is an excellent introduction to NMR techniques. Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*; 2nd ed.; VCH Publishers: New York, 1993.

(180) The signals due to trace amounts of common solvents and impurities could be easily identified.
Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.

(181) Hoye, T. R.; Hanson, P. R.; Vyvyan, J. R. *J. Org. Chem.* **1994**, *59*, 4096.

(182) Hoye, T. R.; Zhao, H. *J. Org. Chem.* **2002**, *67*, 4014.

(183) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(184) Bryan, W. P.; Byrne, R. H. *J. Chem. Educ.* **1970**, *47*, 2923.

(185) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1988.

(186) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

(187) Engler, E. M.; Andose, J. D.; Schleyer, P. V. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005.

(188) Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311-365.

(189) Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **1993**, *93*, 3.

(190) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003-2020.

(191) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726.

(192) Winkler, J. D.; Doherty, E. *J. Am. Chem. Soc.* **1999**, *121*, 7425.